J|A|C|S COMMUNICATIONS

Published on Web 07/15/2009

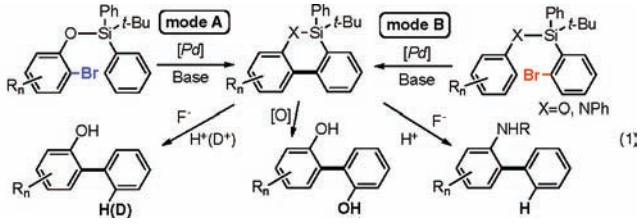
TBDPS and Br-TBDPS Protecting Groups as Efficient Aryl Group Donors in Pd-Catalyzed Arylation of Phenols and Anilines

Chunhui Huang and Vladimir Gevorgyan*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

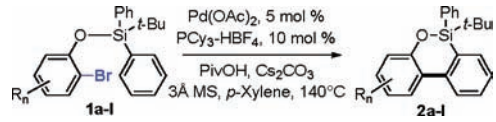
Received June 11, 2009; E-mail: vlad@uic.edu

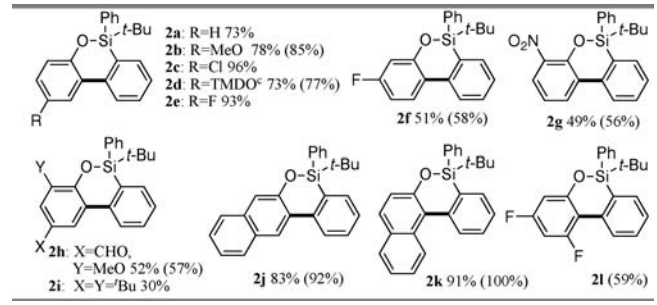
Aryl−aryl bond formation is an important process because of the unique pharmaceutical features and wide applications of biaryls in material science.[1] Traditionally, aryl−aryl bonds are made via cross-coupling reactions between aryl halide (or equivalent) and arylmetal components.[2] Recently, a number of excellent transition-metal-catalyzed direct C−H arylation methodologies have emerged.[3] However, these methods are not without boundaries. Thus, intermolecular versions often suffer from low reactivity and/or regioselectivity, which in some cases can be circumvented by the introduction of a directing group,[3k,4] including a removable directing group.[5] Intramolecular arylations, although much less problematic,[3a,d,6] lead by default to cyclic biaryl products. To the best of our knowledge, there are no reports of the employment of easily removable tethers in the synthesis of biaryls via the C−H arylation motif.[7] Herein, we report that *the common TBDPS protecting group can serve as an efficient aryl group donor for o-bromophenols* via Pd-catalyzed intramolecular arylation followed by a deprotection step (mode A, eq 1). Moreover, it was found that *the newly designed Br-TBDPS protecting group is an even more efficient aryl group donor for simple phenols and anilines* (mode B). Employing this temporary silicon tether motif is beneficial not only because of the ease of its deprotection but also because it provides easy access to deuteriated biaryls and biphenols (eq 1).



The temporary silicon connection method, coined by Stork,[8] has been widely used for rendering intermolecular reactions intramolecular, often resulting in superior regio- and stereoselectivities for these processes.[9] Thus, we reasoned that employing a suitable easily introducible and removable silicon tether may improve the reactivity and regioselectivity of Pd-catalyzed intermolecular C−H arylation reactions (see above). For these studies, we chose phenol, intermolecular arylation of which is a challenging task.[10] Initially, as a removable tether, we chose the *tert*-butyldiphenylsilyl (TBDPS) protecting group, which, since its invention by Hanessian,[11] has enjoyed extensive use in synthesis.[12] We hypothesized that if efficient conditions for intramolecular arylation of silicon-tethered phenyl groups are found, this process would provide a convenient route to ortho-arylated phenols.[10,13] Accordingly, we examined the Pd-catalyzed intramolecular arylation of TBDPS-protected *o*-halophenols **1**. Screening of several sets of standard conditions showed that a modified Fagnou's protocol[3d,14] was the most efficient method for arylation of *o*-bromophenol **1a**.[15,16]

Table 1. Arylation of TBDPS-Protected *o*-Bromophenols (Mode A)[a,b]





[a] See the Supporting Information for the detailed procedure. [b] Isolated yields are given, with NMR yields (against CH_2Br_2 as an internal standard) in parentheses. [c] TMDO = 4,4,5,5-tetramethyl-1, 3-dioxolan-2-yl.

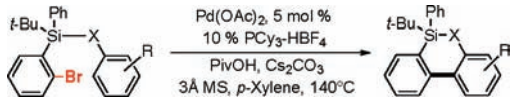
Next, the substrate scope was studied (Table 1). Gratifyingly, it was found that this method is quite general, as diverse substrates possessing MeO, Cl, F, NO_2, and CHO groups were perfectly tolerated under these reaction conditions and produced the corresponding oxasilacycles **2** in good to high yields. The yields were normally higher with electron-rich substrates and somewhat lower with electron-deficient arenes. As expected, highly sterically congested **1i** was less efficient in this reaction.

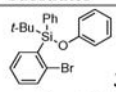
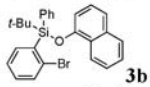
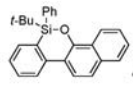
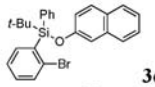
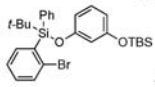
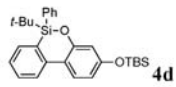
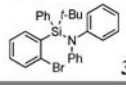
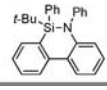
Inspired by a successful employment of the TBDPS group as a tether and, at the same time, a donor of an aryl group to *o*-bromophenols, we aimed at the design of a silyl tether that would allow for arylation of simple phenols (mode B). To this end, we synthesized a Br-TBDPS group[16] and tested it in the Pd-catalyzed arylation of phenols (Table 2). We were pleased to find that the O-Br-TBDPS-protected phenol (**3a**) underwent a nearly quantitative transformation into silacycle **2a** under the same reaction conditions (Table 2, entry 1). Likewise, O-Br-TBDPS-protected 1- and 2-naphthols were cleanly converted into the corresponding cyclization products. O-TBS-protected resorcinol reacted highly regioselectively to give oxasilacycle **4d** in very high yield. Moreover, our initial experiments demonstrated that N-Br-TBDPS-protected anilines also can undergo the Pd-catalyzed intramolecular arylation to give azasilacycle **4e** in good yield![17,18]

Naturally, after the development of efficient intramolecular C−H arylations of silicon-tethered *o*-bromophenols, phenols, and aniline, we performed deprotection of the silicon tether. The standard TBAF deprotection protocol proved successful on oxasilacycles **2** and azasilacycle **4e** to produce arylated phenols **5a** and **5k** and aniline **6** in very high to quantitative yields (eq 2). Moreover, treatment of

10.1021/ja904791y CCC: $40.75

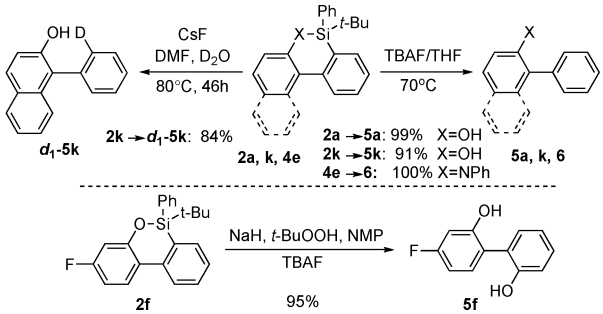
Table 2. Arylation of Br-TBDPS-Protected Phenols (Mode B)[a]



#	Substrates	*t*, (h)	Products	Yield, %[b]
1	 **3a**	0.5	**2a**	99
2	 **3b**	< 3	 **4b**	100
3	 **3c**	1.5	**2k** + **2j**	98 (2.9:1)[c]
4	 **3d**	0.5	 **4d**	97 (10:1)[c]
5	 **3e**	1.5	 **4e**	77

[a] Same conditions as those for mode A. [b] Isolated yield. [c] Major regioisomer shown.

2k with anhydrous CsF in DMF/D_2O led to ***d*$_1$-5k** in 84% yield. Furthermore, employment of modified Woerpel's oxidation conditions[16,19] for **2f** produced unsymmetrical biphenol **5f** in excellent yield!



(2)

In summary, two methods for the Pd-catalyzed arylation of phenols and anilines that employ removable silicon tethers have been developed. It has been shown that the TBDPS protecting group can serve as a convenient aryl group donor for *o*-bromophenols via an intramolecular arylation/deprotection sequence. It has also been shown that the newly designed Br-TBDPS group can serve as an even more efficient aryl group donor for simple phenols and anilines. Remarkably, switching desilylation to oxidation in the last step allows the conversion of the forming silacycles into valuable *o*-biphenols.

Acknowledgment. This work was supported by the National Institutes of Health (Grant GM-64444).

Supporting Information Available: Experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
(2) For a general review, see, for example: *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
(3) For reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. For representative works on biaryl formation, see: (d) Campeau, L.-C.; Parisien, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (e) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (f) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (g) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (h) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (i) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (j) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (k) Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (l) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (m) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (n) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (o) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926. (p) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (q) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (r) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (s) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674. (t) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312.
(4) For directed intermolecular arylation, see: (a) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (b) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (c) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (d) Ackermann, L. *Top. Organomet. Chem.* **2007**, *24*, 35. (e) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (f) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211. (g) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (h) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299.
(5) (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (b) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (c) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159. (d) Giri, R.; Wasa, M.; Breazzano, S. P.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 5685. (e) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (f) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112.
(6) For intramolecular arylations toward biaryls, see: (a) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (c) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (d) Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021.
(7) For cleavage of the cyclic product of intramolecular arylation, see: (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. For arylations proceeding via norbornene-tethered intermediates, see: (b) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512.
(8) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054.
(9) For a review, see, for example: Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813.
(10) Efficient intermolecular arylation of phenols has been reported only on substrates possessing a bulky ortho substituent. See: (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (c) Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Lewis-Alleyne, L. C.; Long, P. D.; Polo-Cerón, D.; Prashar, S. *Chem. Commun.* **2008**, 990.
(11) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(12) (a) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, Germany, 1994. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.
(13) (a) Oi, S.; Watanabe, S.-i.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665. (b) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2. (c) Bajracharya, G. B.; Daugulis, O. *Org. Lett.* **2008**, *10*, 4625. (d) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961.
(14) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.
(15) Iodo- and chlorophenols were less efficient, whereas the corresponding triflates were not stable under these conditions at all.
(16) See the Supporting Information for details.
(17) For a direct intermolecular C−H arylation of anilides, see refs 3h and 3q.
(18) In every case, arylation of a silyl-bound phenyl group of Br-TBDPS (leading to an alternative five-membered silacycle) was not observed.
(19) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044.

JA904791Y