Published in final edited form as:

J Am Chem Soc. 2009 August 12; 131(31): 10844–10845. doi:10.1021/ja904791y.

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

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Abstract

It was shown that the TBDPS protecting group can serve as an efficient phenyl group donor for *o*-bromophenols via the Pd-catalyzed C—H arylation, followed by a routine TBAF deprotection of the forming silacycles. Employment of the newly designed Br-TBDPS protecting group in the same sequence allows for a facile introduction of a phenyl group in the *ortho*-position of phenols and anilines. Alternatively, switching desilylation to oxidation at the last step allows converting the forming silacycles into valuable *ortho*-biphenols.

Aryl-aryl bond formation is an important process due to the unique pharmaceutical features and wide applications of biaryls in material science.¹ Traditionally, the aryl-aryl bond is made via cross-coupling reactions between aryl halide (or equivalent) and aryl metal component.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 often could be circumvented by the introduction of a directing group,^{3k, 4} including a removable directing group.⁵ Intramolecular arylations, although being much less problematic,^{3a,d,6} lead, by default, to cyclic biaryl products. To the best of our knowledge, there are no reports on the employment of easily removable tethers in the synthesis of biaryls via the C-H arylation motif.⁷ Herein, we wish to report that *the common TBDPS protecting group can serve as an efficient aryl group donor for o-bromophenols* via the 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 even more efficient aryl group donor for simple phenols and anilines* (mode B). Not only employment of this temporary silicon tether motif is beneficial due to the easiness of its deprotection, but also due to the fact that it provides easy access to deuteriated biaryls and biphenols (eq 1).

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

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

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, NO₂ and CHO groups, were perfectly tolerated under these reaction conditions to produce 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. Expectedly, the highly sterically-congested **1i** was less efficient in this reaction.

Inspired by a successful employment of TBDPS group as a tether and, at the same time, a donor of an aryl group for *o*-bromophenols, we aimed at the design of a silyl tether that will allow for arylation of simple phenols (mode B). To this end, we synthesized a Br-TBDPS group¹⁶ 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**), under the same reaction conditions, underwent a nearly quantitative transformation into silacycle **2a** (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 development of efficient intramolecular C-H arylations of silicon-tethered *o*-Br-phenols, phenols, and aniline, we performed deprotection of the silicon tether. Thus,

standard TBAF deprotection protocol proved successful on oxasilacycles **2** and azasilacycle **4e** to produce arylated phenols **5a**, **5k**, and aniline **6** in very high to quantitative yields (eq 2). Moreover, treatment of **2k** with anhydrous CsF in DMF/D₂O lead to **d₁-5k** in 84 % yield. Furthermore, employment of a modified Woerpel's oxidation conditions^{16,19} for **2f** produced unsymmetrical biphenol **5f** in excellent yield!

(2)

In summary, two methods employing a removable silicontether for the Pd-catalyzed arylation of phenols and anilines have been developed. It was shown that the TBDPS protecting group could serve as a convenient aryl group donor for *ortho*-bromophenols via an intramolecular arylation/deprotection sequence. It was also shown that the newly designed Br-TBDPS group could serve as an even more efficient aryl group donor for simple phenols and anilines. Remarkably, switching desilylation to oxidation at the last step allows converting the forming silacycles into valuable *orthobiphenols*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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

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16. See Supporting Information for details.
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Table 1
Arylation of TBDPS-Protected *o*-Br-Phenols (Mode A)^{a,b}

 1a-l	 2a-l
 2a: R=H 73%	 2b: R=MeO 78% (85%)
 2c: R=Cl 96%	 2d: R=TMDO ^c 73% (77%)
 2e: R=F 93%	 2f 51% (58%)
 2g 49% (56%)	
 2h: X=CHO, Y=MeO 52% (57%)	 2j 83% (92%)
 2i: X=Y= ^t Bu 30%	 2k 91% (100%)
	 2l (59%)

^a See Supporting Information for the detailed procedure.

^b Isolated yield, NMR yield against CH₂Br₂ as internal standard in the parenthesis.

^c TMDO = 4,4,5,5-tetramethyl-1,3-dioxolan-2-yl.

Table 2
Arylation of Br-TBDPS-Protected Phenols (Mode B)^a

#	Substrates	<i>t</i> , (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.