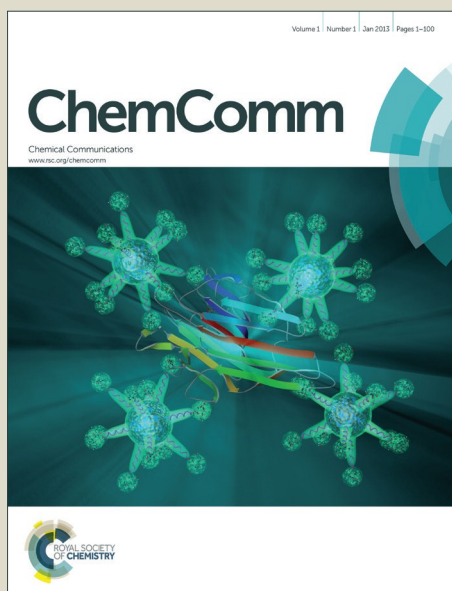


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ARTICLE TYPE

Palladium-Catalyzed Silylation Reaction between Benzylic Halides and Silylboronate

Zhi-Dao Huang,^a Ran Ding,^a Peng Wang,^{*c} Yun-He Xu,^{*a} and Teck-Peng Loh^{a,b}

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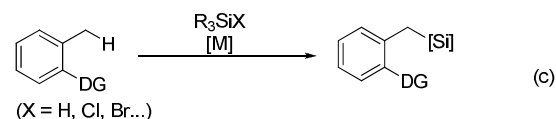
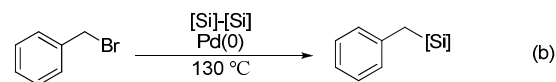
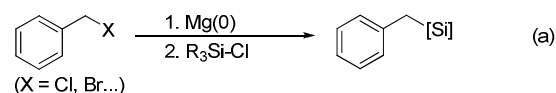
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An efficient Pd-catalyzed silylation reaction of benzylic halides with silylboronate is reported. In this reaction, primary and secondary benzylic halides could react well with silylboronates to afford benzylic silanes. This reaction accommodates a broad substrate scope and proceeds smoothly under very mild reaction conditions. The corresponding products could be obtained in moderate to high yields and with stereospecificity.

Organosilicon fragments are widely observed or used in synthesis of bioactive molecules and organic materials.^[1] Therefore, the development of efficient methods for the synthesis of various organosilicon compounds has attracted much attention from organic chemists.^[2] Accordingly, various noble transition-metal catalyzed hydrosilylation of unsaturated carbon-carbon bonds using silanes have been well developed to afford organosilicon compounds.^[3] Recently, the methods of direct C–H bond silylation reaction catalyzed by transition-metal catalysts have emerged gradually as powerful tools for the construction of C–Si bonds.^[4] Therefore, useful organosilicon products could be prepared *via* these practicable methods. However, among the established methodologies, the preparation of benzylic silanes still faces some challenges such as limited substrate scope and/or harsh reaction conditions *etc.* Traditionally, the most popular synthetic route to access this kind of products is reacting the Grignard reagents with silyl halides (Scheme 1, (a)).^[5] However, substrates with functional groups such as carbonyls, cyano and other strong electron-withdrawing groups could not be tolerated which greatly restricts its wide application in organic synthesis. Another strategy to synthesize these products was conducted by using palladium catalyst and disilanes (Scheme 1, (b)).^[6] However, only limited substrates have been examined at high temperature. Recently, few examples on benzylic C–H bond silylation reactions with the help of directing groups have also been elegantly developed (Scheme 1, (c)).^[7] Noticeably, He and co-workers reported the first Pd-catalyzed silylation reaction between aryl pivalates and silylboronate.^[10b] In continuation of our interest in development of C–Si bond formation,^[8] herein we would like to report a palladium-catalyzed

Scheme 1. Different methodologies for benzylic silylation reactions.

Previous work:



This work:

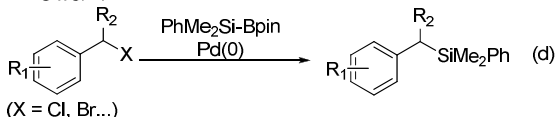
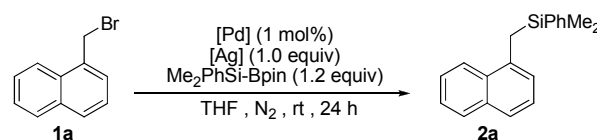


Table 1. Optimization of reaction conditions between 1- (bromomethyl)naphthalene and silylboronate PhMe₂SiBpin.^[a]



entry	[Pd]	[Ag]	solvent	yield (%)
1 ^b	Pd(PPh ₃) ₄	Ag ₂ O	THF	93
2 ^b	Pd(PPh ₃) ₂ Cl ₂	Ag ₂ O	THF	64
3 ^b	Pd ₂ (dba) ₃	Ag ₂ O	THF	trace
4	Pd(PPh ₃) ₄	Ag ₂ O	THF	70
5	Pd(PPh ₃) ₄	Ag ₂ CO ₃	THF	42
6	Pd(PPh ₃) ₂	AgTFA	THF	trace
7 ^c	Pd(PPh ₃) ₄	AgOAc	THF	85 ^d
8 ^c	Pd(PPh ₃) ₂	AgOAc	THF	75
9	Pd(PPh ₃) ₄	AgOAc	Et ₂ O	78
10	Pd(PPh ₃) ₄	AgOAc	DCM	52
11 ^f	Pd(PPh ₃) ₄	/	THF	27
12 ^g	Pd(PPh ₃) ₄	Ag ₂ O	THF	85 ^d
13	/	Ag ₂ O	THF	0
14	Pd(PPh ₃) ₄	/	THF	0

^a All the reactions were carried out with **1a** (1.0 equiv, 0.2 mmol), solvent (2 mL), yield was determined by ¹H NMR using mesitylene as internal standard. ^b The amounts of [Pd] was 5 mol%. ^c This condition was not suitable for the other substrates. ^d Isolated yield. ^e NaOAc (1.0 equiv) was used as an additive. ^f K₂CO₃ (1.0 equiv) was added. ^g The amounts of [Pd] was 2 mol%.

^a Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China.

^b Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

^c Department of Chemical Engineering and Technology, Tianshui Normal University, Tianshui, 741000, China.

E-Mail: xyh0709@ustc.edu.cn; w.p.david@139.com

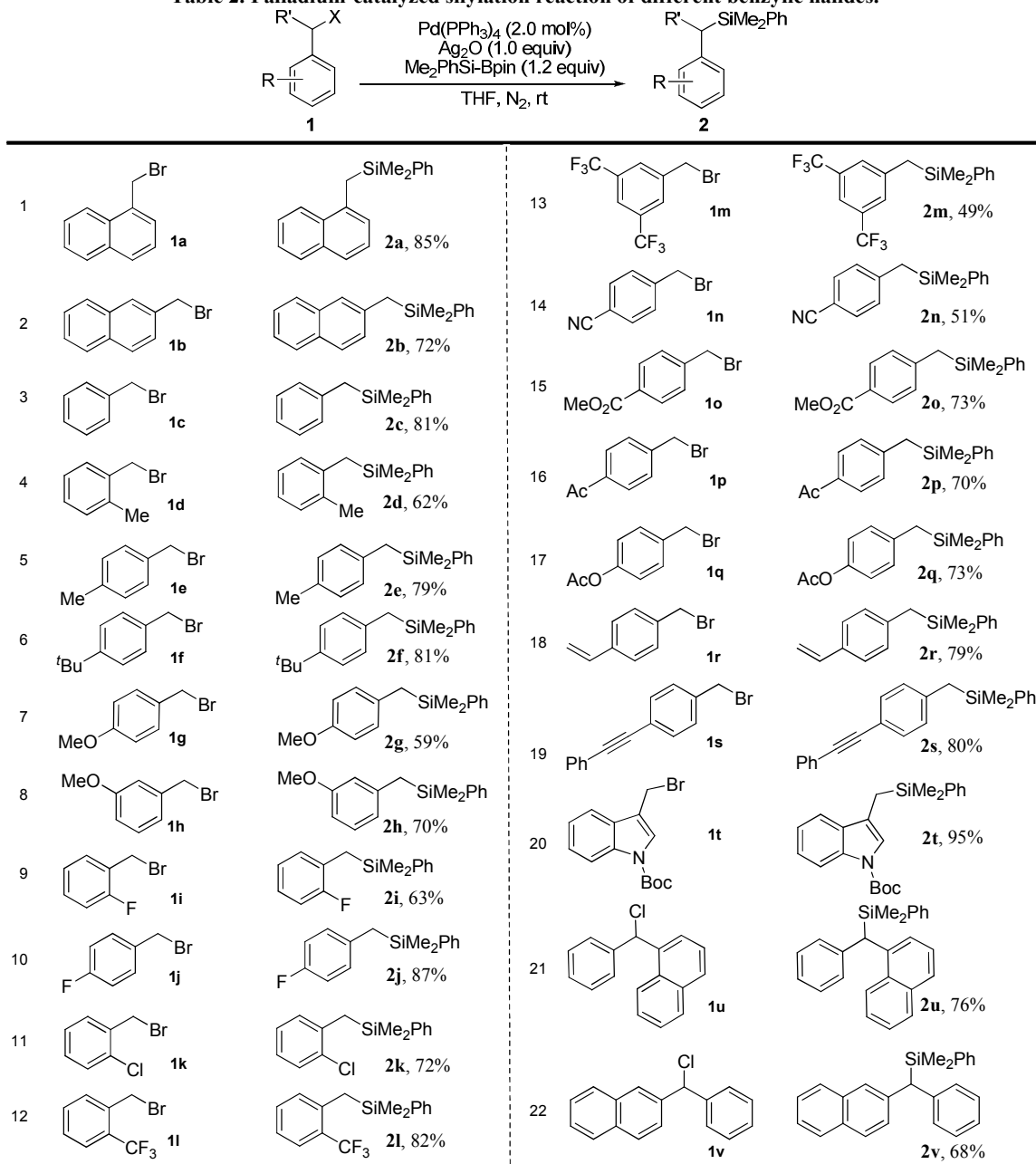
benzylic silylation reaction using easily available benzylic halides and silyboronate^[9] as starting materials.^[10]

At the beginning, 1-(bromomethyl)naphthalene **1a** and silyboronate PhMe₂SiBpin were reacted with different palladium catalysts (entries 1-3, Table 1), and it was found that Pd(PPh₃)₄ was highly efficient to provide the desired product in the presence of silver oxide in THF solution (entry 4, Table 1). Further screening showed that changing of silver additives or solvents could not afford better results (entries 5-10, Table 1). Finally, the desired product **2a** still could be obtained in high yield by reducing the catalyst loading to 2 mol% (entry 12, Table 1). Control experiments were carried out, and the results showed that no any desired product could be detected in the absence of

palladium catalyst (entry 13, Table 1) or silver oxide (entry 14, Table 1).

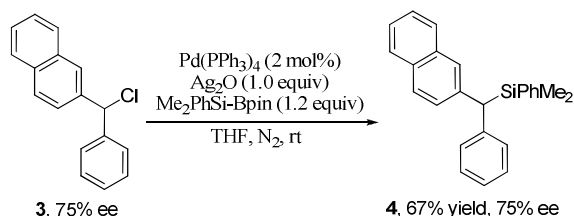
With the optimized reaction conditions in hand, various benzylic halides were tested in this reaction. The results are summarized in Table 2. It could be observed that in most cases the benzylic bromide bearing either electron-donating or electron-withdrawing group all afforded the desired products in high yields (entries 1-8, Table 2). Although only moderate yield of the product **2m** was obtained (entry 13, Table 2), the highly electron-deficient 1-(bromomethyl)-3,5-dinitrobenzene **1m** still could be employed in this reaction. Moreover, it is worthy noting that some groups such as acetal, ester and cyano *etc.*, being sensitive in traditional methods, could all be tolerated in this reaction

Table 2. Palladium-catalyzed silylation reaction of different benzylic halides.



All the reactions were carried out with **1** (1.0 equiv, 0.3 mmol), Pd(PPh₃)₄ (2.0 mol%), Ag₂O (1.0 equiv), silyboronate (1.2 equiv) in THF (2 mL) under an atmosphere of N₂ at room temperature. For **1a-1h**, **1q-1v**, the reactions ran for 24 h. For **1i-1p**, the reactions ran for 36 h. All yields were isolated yields after silica chromatography.

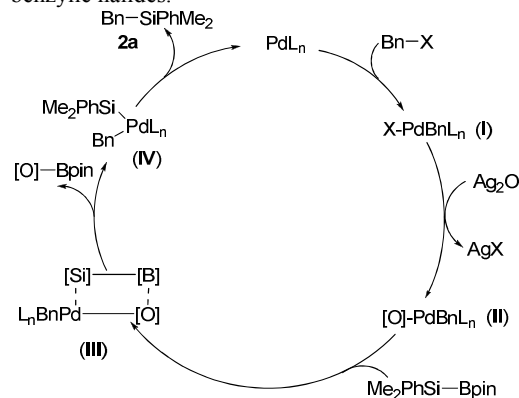
(entries 14, 15 and 16, Table 2). Importantly, the terminal alkene and internal alkyne fragment on substrates remain intact in the presence of palladium catalyst (entries 18 and 19, Table 2). Finally, Boc-protected 3-(bromomethyl)-indole (entry 20, Table 2) and secondary benzyl chloride (entries 20 and 21, Table 2) were applied in this silylation reaction, the corresponding products could all be isolated in good yields. Therefore, this method provides a practical pathway to prepare benzyl silanes compared to the traditional synthetic routes.



After successful synthesis of various benzyl silane compounds, we next turned our attention to explore the possible mechanism of this catalytic silylation reaction. An enantioenriched 2-(chloro(phenyl)methyl)naphthalene **3** was prepared and subjected to this coupling reaction. It was found that the desired silylation product **4** could be obtained in 67% yield and with retention of substrate's enantiopurity.

With this observed result, a plausible mechanistic pathway was proposed as shown in Scheme 1. Firstly, the C-X bond could be activated by Pd(0) catalyst and a Pd(II) intermediate **I** was generated. Following, a palladium species (**II**)^[11] could be formed in the presence of silver oxide which would facilitate the activation of Si-B bond and transmetalation process to give intermediate **IV**. Finally, the desired product could be generated after reductive elimination and released the Pd(0) catalyst to next catalytic cycle.

Scheme 2. Proposed mechanism for the Pd-catalyzed silylation of benzylic halides.



Conclusions

In conclusion, we have developed an efficient methodology of palladium-catalyzed silylation reaction of benzylic halides. Various benzyl silanes could be obtained in good yields by using only 2 mol% of palladium catalyst at room temperature. The wide scope of the functional groups tolerated in the substrates will allow this method to be a general and powerful tool for synthesis of benzyl silane compounds. Moreover, the retention of enantiopurity in the enantioenriched substrate during transformation could be achieved in this reaction. Further

investigations of this strategy to carry out other organic transformations are currently underway.

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