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Palladium-Catalyzed Direct Benzylation of Azoles with Benzyl Carbonates

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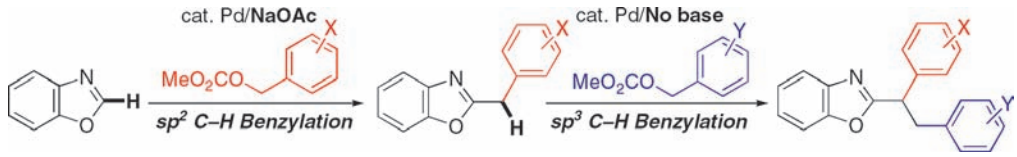
ABSTRACT



The direct aromatic sp² C−H benzylation of azole compounds with benzyl carbonates proceeds efficiently in the presence of a $Pd_2(dba)_3$/dppp catalyst system and NaOAc as a base to afford the corresponding diarylmethanes in good yields. In addition, the same palladium catalyst enables the direct benzylic sp³ C−H benzylation with the second benzyl carbonates without employing any external base.

Diarylmethanes are ubiquitously found in pharmaceuticals and biologically active compounds[1] and employed as subunits in the design of supramolecular structures.[2] A useful and classical approach to these units is Lewis acid mediated Friedel−Crafts or S_EAr reactions with arenes and benzylic electrophiles.[3] However, these processes often encounter difficulty in controlling regio- and chemoselectivity of the reaction and are restricted in substrate scope to the electron-rich arenes. As alternative methods, the 1,2-addition of organometallic reagents to aromatic aldehydes/reduction of the obtained carbinols sequences[4] or transition-metal-catalyzed cross-coupling reactions of benzylic halides or pseudohalides with arylmetals[5] are most popular and compensate for the lack of generality mentioned above. In addition, recent advances in the metal-catalyzed direct C−H functionalization[6] provide a potentially more powerful and facile access to these target molecules since the preactivation step of arenes can be obviated. So far, Hoarau,[7] Fagnou,[8] and Ackermann[9] have independently developed direct benzylation methodologies of heteroarenes and directing-group-containing arenes under palladium[10] or ruthenium[11] catalysis.

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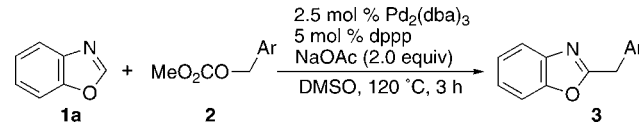
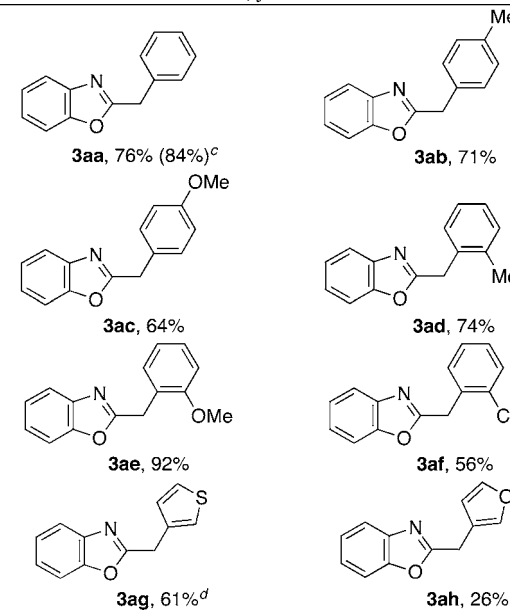
While valuable, the benzyl sources are still limited to the highly reactive benzyl chlorides or bromides. The displacement of them with readily accessible, stable, and easy-to-handle carbonates[12] is quite appealing. Here, we report the aromatic sp^2 C−H benzylation of azoles with benzyl carbonates using a simple palladium catalyst, $Pd_2(dba)_3$/dppp, and a mild base such as NaOAc.[13] Moreover, the same palladium catalyst without additional base is found to be effective for the direct benzylation of the benzylic sp^3 C−H bonds.

In a typical experiment, treatment of benzoxazole (**1a**) with benzyl methyl carbonate (**2a**) in the presence of 2.5 mol % of $Pd_2(dba)_3$, 5 mol % of dppp, and 2.0 equiv of NaOAc in DMSO (5.0 mL) at 120 °C for 3 h afforded the corresponding benzylated product **3aa** in 76% yield (Table 1).[14] A variety of benzyl carbonates were tested for the direct benzylation of benzoxazole (**1a**). The carbonates with electron-donating methyl **2b** and methoxy groups **2c** resulted in the formation of **3ab** and **3ac** in good yields. Sterically demanding *ortho* substitution pattern was tolerant toward the direct benzylation (**3ad** and **3ae**). In particular, 2-methoxybenzyl carbonate **2e** coupled with **1a** very smoothly to furnish **3ae** in 92% yield. The reaction with **2f** produced **3af** in an acceptable yield with the carbon-chloride moiety left intact, which could enjoy further manipulation. The heteroaryl function, a thienylmethyl group, also could be introduced to the benzoxazole core (**3ag**). On the other hand, the furan derivative **2h** showed lower reactivity (**3ah**). Notably, the catalytic reaction on a 5-fold larger scale was possible, indicating the good reliability of the process (**3aa**).

Table 1. Palladium-Catalyzed Direct Benzylation of Benzoxazole (**1a**) with Various Benzyl Methyl Carbonates **2**[a]



3, yield[b]



[a] A mixture of **1a** (0.50 mmol), **2** (1.0 mmol), $Pd_2(dba)_3$ (0.013 mmol), dppp (0.025 mmol), and NaOAc (1.0 mmol) was stirred in DMSO (5.0 mL) at 120 °C for 3 h. **2a**: Ar = Ph. **2b**: Ar = 4-MeC_6H_4. **2c**: Ar = 4-$MeOC_6H_4$. **2d**: Ar = 2-MeC_6H_4. **2e**: Ar = 2-$MeOC_6H_4$. **2f**: Ar = 2-ClC_6H_4. **2g**: Ar = 3-thienyl. **2h**: Ar = 3-furyl. [b] Isolated yield. [c] Yield in a 5-fold larger scale is in parentheses. [d] With 1.5 mmol of NaOAc for 6 h.

Next, we performed the benzylation with an array of azoles utilizing the $Pd_2(dba)_3$/dppp/NaOAc system (Figure 1). The benzoxazoles bearing methyl, phenyl, and chloro substituents at the 5-position as well as the simple one could be transformed to the corresponding products **3ba**, **3ca**, and **3da** in 63%, 68%, and 39% yields, respectively. In addition, 1,3,4-oxadiazole, which has received much attention in pharmaceutical and materials chemistry,[15,16] was found to be suitable substrate. Although a trend that electron-withdrawing trifluoromethylphenyl and bulky naphthyl substitutions at the 2-position decreased the yields (**3ha** and **3ia**) was observed, various substrate combinations were available for use. On the other hand, the reaction with 5-aryloxazoles

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(14) See Supporting Information for the optimization studies.

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and benzothiazole proceeded sluggishly under the standard conditions. Some additional investigation revealed that the modification of ligand or base was essential, and the coupling products **3ka**, **3la**, and **3ma** were obtained albeit with the moderate yields.

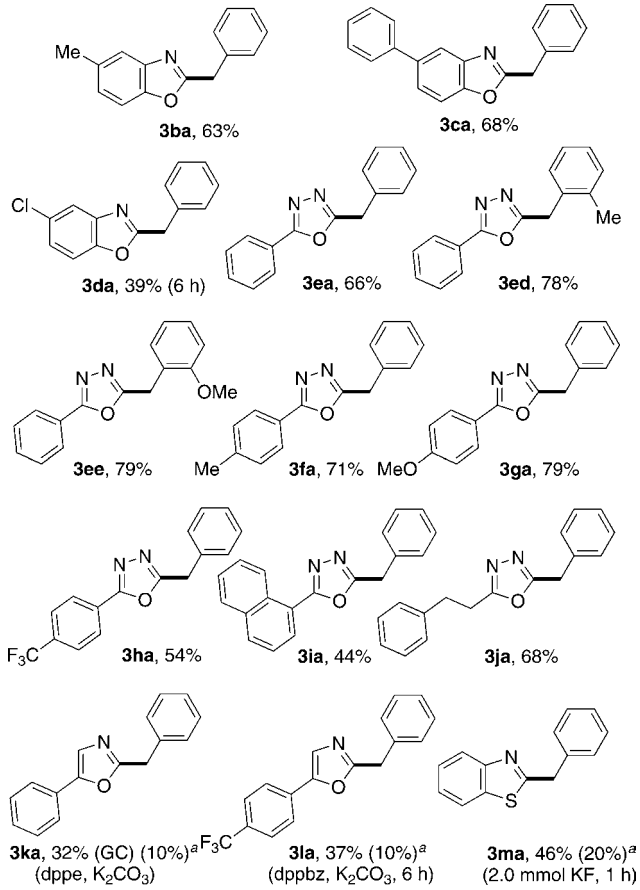


Figure 1. Direct benzylation with various azoles. [a]Yield was determined by GC methods under the standard reaction conditions using dppp and NaOAc.

During our optimization studies for the direct coupling of **1a** with **2a**, we serendipitously detected the double benzylation product **4aa** by GC analysis (Scheme 1). Apparently, the initially formed **3aa** underwent the second benzylation. With the preliminary interesting finding, we focused on the direct benzylic sp^3 C−H benzylation of **3aa**.[17] The detailed survey of palladium salts, ligands, and bases indicated that, to our surprise, the simple removal of base from the reaction medium proved to be optimal, leading to the desired **4aa** in 69% yield (Table 2). As illustrated in Table 1, various benzyl carbonates were applicable to the coupling with **3aa** to furnish the benzylated diarylmethanes in moderate to good yields. It is noteworthy that benzothiazole derivative **3ma** also took part in the direct benzylic functionalization (**4aa′**).

(17) Palladium-catalyzed direct arylation of benzylic sp^3 C−H bonds with aryl halides: (a) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373. (b) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (c) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155.

Scheme 1

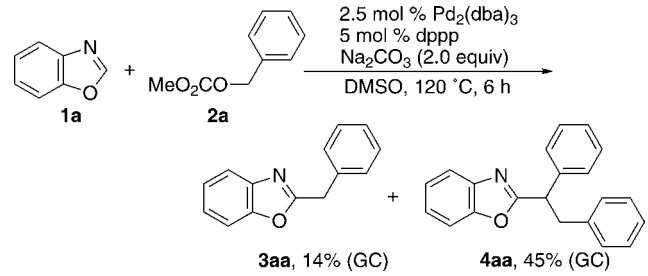
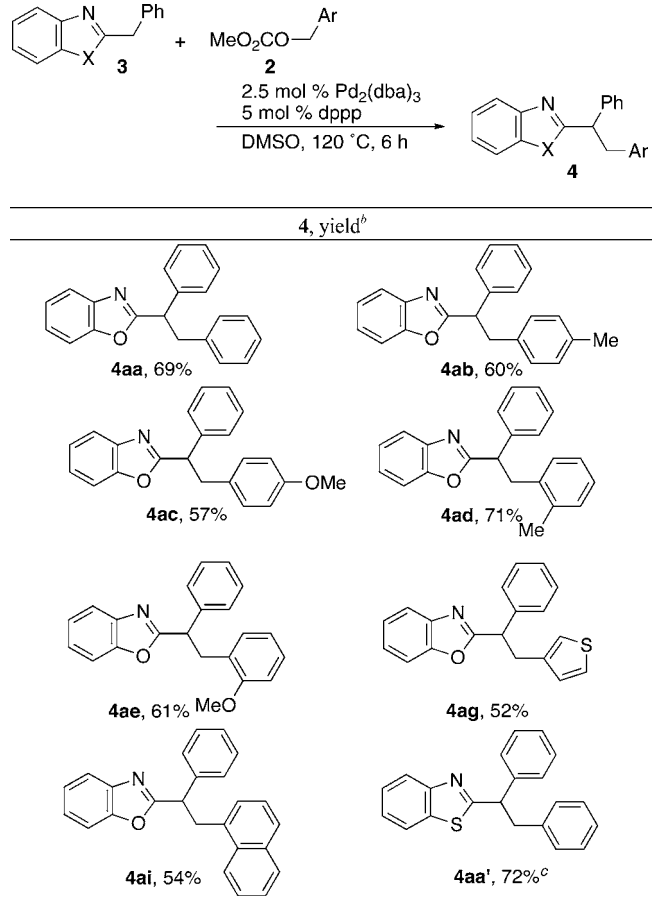


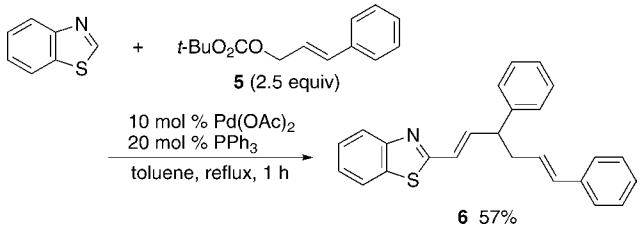
Table 2. Palladium-Catalyzed Direct Benzylic sp^3 C−H Benzylation of 2-Benzylazoles **3** with Benzyl Carbonates **2**[a]



[a] A mixture of **3** (0.50 mmol), **2** (0.60 mmol), $Pd_2(dba)_3$ (0.013 mmol), and dppp (0.025 mmol) was stirred in DMSO (5.0 mL) at 120 °C for 6 h. **3aa**: X = O. **3ma**: X = S. **2a**: Ar = Ph. **2b**: Ar = 4-MeC_6H_4. **2c**: Ar = 4-$MeOC_6H_4$. **2d**: Ar = 2-MeC_6H_4. **2e**: Ar = 2-$MeOC_6H_4$. **2g**: Ar = 3-thienyl. **2i**: Ar = 1-naphthyl. [b] Isolated yield. [c] At 140 °C.

Finally, we examined the reactivity of cinnamyl carbonate **5** electronically related to the benzyl carbonate **2**. On exposure of **5** to a solution of benzothiazole in toluene under $Pd(OAc)_2/2PPh_3$ catalysis, the double allylation analogous to the benzylation described above occurred to form the azole-containing 1,5-hexadiene **6** in 57% yield (Scheme 2). While further modification is required, the methodology would have high potential for the synthesis of multisubsti-

Scheme 2



tuted 1,5-hexadienes, which is relatively challenging by the conventional cross-coupling strategies.[18]

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In summary, we have described an effective palladium catalyst system for the direct benzylation of the aromatic sp^2 C−H bond of azoles with benzyl carbonates easily derived from the corresponding benzyl alcohols. In addition, the simple removal of the external base allowed the same palladium complex to catalyze the benzylic sp^3 C−H benzylation. The catalytic process compliments the precedent direct benzylation reactions[7−9] and provides a concise route to the diarylmethanes of interest in both medicinal and material chemistry.

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Supporting Information Available: Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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