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Copper-Catalyzed Direct Benzylation or Allylation of 1,3-Azoles with *N*-Tosylhydrazones

Xia Zhao, Guojiao Wu, Yan Zhang, and Jianbo Wang*

Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

Supporting Information

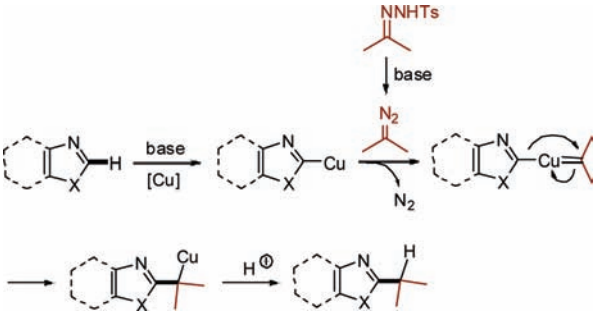
ABSTRACT: Cu-Catalyzed cross-coupling of *N*-tosylhydrazones with 1,3-azoles leads to the direct C−H benzylation or allylation. Cu carbene migratory insertion is proposed to play the key role in this transformation.

1,3-Azoles have found wide applications as structure motifs in natural products, pharmaceutically active compounds, agrochemicals, and organic functional materials such as liquid crystals and fluorescent dyes.[1] Over the many decades, enormous efforts have been devoted to the development of efficient methods for synthesizing this type of aromatic heterocycles, especially those with appropriate substitutions.[2] In this context, transition-metal-catalyzed C−H functionalizations of heterocycles have witnessed explosive developments in the past few years due to their advantages over the traditional coupling approaches, in which not easily available heteroaromatic organometallic reagents have to be employed.[3] Up to now, most of the studies on direct C−H functionalization are focused on the direct arylation of 1,3-azoles, namely the formation of sp^2-sp^2 C−C bonds.[4−9] These direct arylations are supposed to proceed through similar reaction mechanisms, which include initial deprotonation of a relatively acidic sp^2 C−H bond of heterocycles by an alkali metal base, oxidative addition, transmetalation and reductive elimination.[10] A wide range of metal catalysts, including palladium,[4,7d,8a,b,d] copper,[5,7f] rhodium,[6d,e] ruthenium,[6h] cobalt[6g] and nickel,[6a,b,7e,8e] have been exploited for these catalytic processes. Among these transition metal catalysts, inexpensive copper salts are particularly attractive due to their potential applicability in industry.

Despite tremendous developments in direct C−H arylation, the transition-metal-catalyzed cross-coupling of heteroarene C−H bonds with sp^3 carbon remains largely unexploited.[9] Direct benzylation of heteroarenes and directing-group-containing arenes have been recently developed by Hoarau,[11a] Fagnou[9c] and Ackermann.[11b] Very recently, Miura reported a Pd-catalyzed direct benzylation of 1,3-azoles with benzyl carbonates,[9b] and Nakao and Hiyama reported a Ni-catalyzed hydroheteroarylation of vinylarenes.[12] We have noted that in most of the previously reported direct benzylation reactions, only primary benzylation is achieved except for the Ni-catalyzed reaction reported by Nakao and Hiyama. This inflicts significant limitations on these methodologies. It can be anticipated that β-hydride elimination may become a problem when secondary benzyl halides are employed as coupling partners.

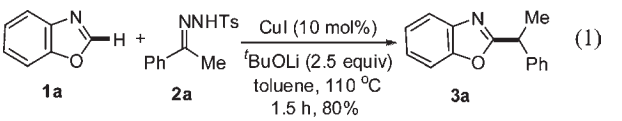
Recently, we developed a copper-catalyzed cross-coupling reaction of *N*-tosylhydrazones with terminal alkynes, which afforded allene products.[13] It has been supposed that the reaction is initialized with deprotonation of the relatively acidic terminal alkyne. Subsequent transmetalation and dediazotization of the in situ-generated diazo substrate lead to the formation of a Cu carbene species, which undergoes a migratory insertion process.[14]

Scheme 1. Cu-Catalyzed Reaction of 1,3-Azole with *N*-Tosylhydrazone



We conceived that the heteroaromatics bearing similar acidic C−H bonds as those of terminal alkynes, may also be suitable cross-coupling partners to couple with *N*-tosylhydrazones under similar Cu-catalyzed conditions (Scheme 1). We found that this was indeed the case, and we report herein a highly efficient Cu(I)-catalyzed direct benzylation or allylation of heteroaromatic compounds with *N*-tosylhydrazones. Mechanistically, this direct C−H bond functionalization process is fundamentally different from those recently reported in the literature. Moreover, a transition-metal-catalyzed direct C−H functionalization of heteroaromatics with secondary benzyl groups is achieved.

At the outset of this investigation, we explored the Cu-catalyzed reaction of benzo[*d*]oxazole **1a** and *N*-tosylhydrazone **2a** (eq 1). After extensive screening of the reaction conditions (the copper salts, ligands, solvent, base, and temperature),[15] it was concluded that under the following reaction conditions the expected product **3a** could be obtained in good yield: CuI as catalyst and ^{t}BuOLi as base in toluene at 110 °C.



(1)

With the optimized reaction conditions established, the scope of this transformation was subsequently investigated. The examples of the reactions between oxazoles and *N*-tosylhydrazones

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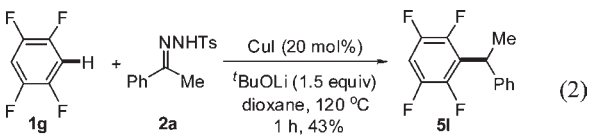
are presented in Figure 1. The reaction could be carried out with a series of substituted aryl *N*-tosylhydrazones **2a**−**u** and oxazoles **1a**−**e**, affording the corresponding products **3a**−**s** and **4a**−**h** in moderate to good yields.

The reaction was found not significantly affected by the substituents on the aromatic ring of *N*-tosylhydrazones. Both electron-donating and electron-withdrawing groups were tolerated under the reaction conditions (Figure 1, 3a−e). The reaction is also not noticeably affected by the position of the substituents on the aromatic ring of aryl *N*-tosylhydrazones. However, the reaction of benzo[*d*]oxazole **1a** with **2j** only afforded the product **3j** in 46% yield under the standard conditions. This diminished yield is attributed to the formation of (*E*)-1,2-diphenylethene, which is derived from 1,2 hydrogen shift of carbene intermediate. This side reaction seems not avoidable under the standard conditions, but the yield of the expected product could be improved by simply changing the substrate ratio of **1a** to **2j** from 1.0: 1.2 to 1.0: 2.0.

This reaction proceeded smoothly with other substituted benzo[*d*]oxazoles (Figure 1, 3k-q and 4h). The reaction was not affected by the substituents on the phenyl ring of benzo-[*d*]oxazoles. However, slightly diminished yields were observed for the reaction with 5-phenyloxazole (Figure 1, 3r, s). The reaction also proceeded smoothly with *N*-tosylhydrazones derived from diaryl ketones, affording the corresponding benzylation products **4a-d** in moderately high yields. Moreover, the *N*-tosylhydrazone derived from benzaldehyde was also suitable substrate for the reaction, affording **4e** in 53% yield.

We also applied this reaction system to the direct allylation. Thus, the *N*-tosylhydrazones derived from 3-methylcyclohex-2-enone and 4-methylpent-3-en-2-one were subjected to the slightly modified reaction conditions with increased loading of catalyst CuI (20 mol %). Allylation products **4f-h** could be obtained in moderate yields.

Encouraged by the results obtained with oxazoles, we proceeded to apply this catalytic system to other aromatic heterocycles with similar acidic C−H bond. However, direct benzylation of aromatic heterocycles such as benzofuran, benzo[*b*]thiophene, and benzo-[*d*]imidazole under similar conditions with *N*-tosylhydrazone did not proceed well.[15] To our delight, it was found that thiazoles could be employed in this benzylation reaction, with increased catalyst loading and with dioxane as solvent. The requirement for the higher catalyst loading as compared to the reaction for oxazoles is assumed to be due to the relatively lower activity of the C−H bond of thiazoles. A series of *N*-tosylhydrazones **2a**, **2h**, **2i**, **2m**, **2o**, **2v**−**y** and thiazoles **1f**, **g** were tested, giving product **5a**−**k** in moderate to high yields (Figure 2). It is worthy to note that the reaction is substantially affected by the loading of CuI catalyst. For example, as shown by the synthesis of **5d**, the yield could be improved by using 30 mol % of CuI catalyst. Finally, we were delighted to find that benzylation of 1,2,4,5-tetrafluorobenzene **1g** also worked, albeit with low efficiency (eq 2).[16]



(2)

A possible mechanism for this novel direct C−H bond benzylation has been depicted in Scheme 1. The key step in the reaction is the migratory insertion of Cu carbene species. We have proposed a Cu carbene migratory insertion in our previous publication on Cu-catalyzed coupling of terminal alkyne and *N*-

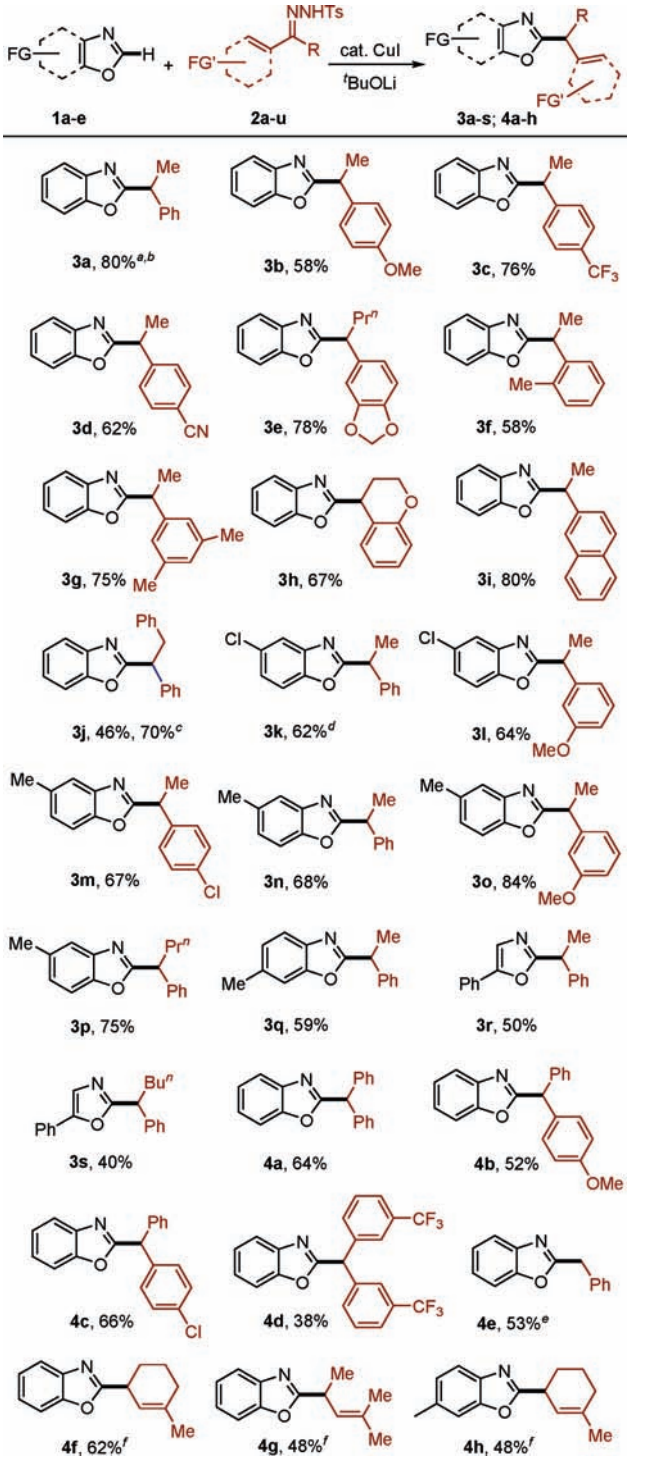


Figure 1. Cu-Catalyzed benzylation of oxazoles with *N*-tosylhydrazones. Reaction conditions if not otherwise noted: [a] **1a**−**e** (0.5 mmol), **2a**−**u** (0.6 mmol), CuI (10 mol %), ^{t}BuOLi (1.25 mmol), toluene (2.0 mL), 110 °C, 1.5 h. [b] All the yields refer to isolated product after chromatography with silica gel if not otherwise noted. [c] The reaction was carried out under these conditions: **1a** (0.5 mmol), **2j** (1.0 mmol), CuI (10 mol %), LiO^tBu (1.75 mmol), toluene (2.0 mL), 110 °C, 1.5 h. [d] Yield of isolated product after chromatography with neutral Al_2O_3. [e] Reaction conditions: **1a** (0.5 mmol), **2s** (1.0 mmol), CuI (20 mol %), ^{t}BuOLi (1.75 mmol), dioxane (2.0 mL), 120 °C, 1.5 h. [f] Reaction conditions: **1a**, **1c** (0.5 mmol), **2t**, **2u** (0.6 mmol), CuI (20 mol %), ^{t}BuOLi (1.25 mmol), toluene (2.0 mL), 110 °C, 1.5 h.

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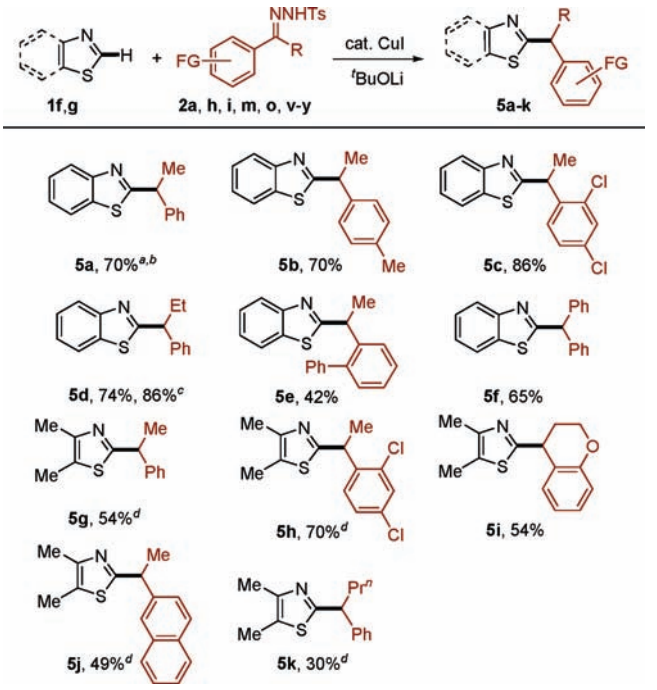
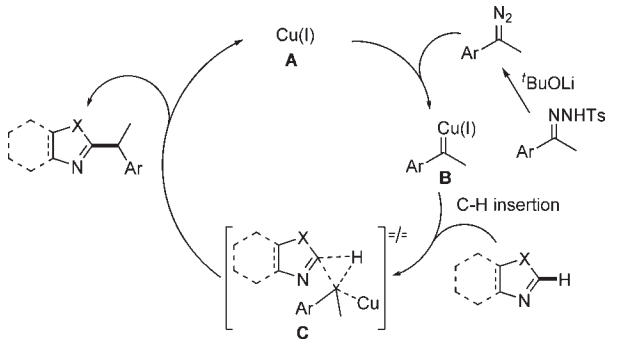


Figure 2. Cu-Catalyzed benzylation of thiazoles with *N*-tosylhydrazones. Reaction conditions if not otherwise noted: [a] **1e** (0.5 mmol), **2** (0.6 mmol), CuI (20 mol %), ^{t}BuOLi (1.25 mmol), dioxane (2.0 mL), 120 °C, 1 h. [b] Yield of isolated product after chromatography with silica gel. [c] **1e** (0.5 mmol), **2x** (0.6 mmol), CuI (30 mol %), ^{t}BuOLi (1.25 mmol), dioxane (2.0 mL), 120 °C, 1 h. [d] Reaction conditions: **1g** (0.75 mmol), **2a**, **h**, **i**, **m**, **v** (0.5 mmol), CuI (20 mol %), ^{t}BuOLi (1.25 mmol), dioxane (2.0 mL), 110 °C, 1.5 h.

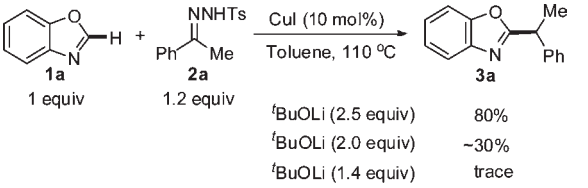
Scheme 2. Proposed C−H Bond Insertion Mechanism



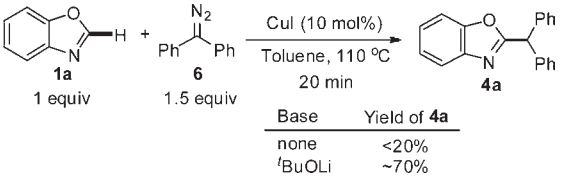
tosylhydrazone.[13] However, for the direct C−H bond benzylation described in this paper, an alternative mechanism which involves a direct Cu carbene insertion into C−H bond of heterocycles cannot be strictly eliminated (Scheme 2).[17]

To gain insight into the reaction, several control experiments were carried out. First, we studied the effect of the amount of base on the reaction (Scheme 3). If the reaction follows the Cu carbene insertion mechanism, theoretically only 1 equiv of the base, required for converting the *N*-tosylhydrazone into diazo substrate, is sufficient for completing the benzylation reaction. It was observed that the yield of benzylation product was significantly diminished when the amount of base was reduced to less than 2.0 equiv. The benzylation product was only formed in trace amount when the base was reduced to 1.4 equiv.

Scheme 3. Effect of the Amount of Base on the Reaction

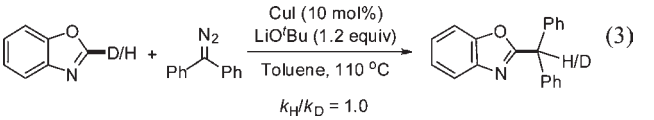


Scheme 4. Benzylation of 1a with Diphenyldiazomethane 6



Next, diphenyldiazomethane **6** was synthesized and was subjected to the benzylation reaction (Scheme 4). In the absence of base, less than 20% of the benzylation product **4a** was identified under the otherwise standard reaction conditions, whereas the yield could be increased to 70% when the same reaction was carried out in the presence of 1.2 equiv of base.

Moreover, we found that the reaction did not show kinetic isotope effect (eq 3). If the reaction follows a Cu carbene insertion mechanism as depicted in Scheme 2, kinetic isotope effect may be expected since the C−H insertion process is considered to follow a concerted reaction mechanism.[18] Conversely, if the Cu carbene migratory insertion mechanism as shown in Scheme 1 operates, this result can be reasonably explained by considering the stepwise reaction mechanism, in which the deprotonation is a fast equilibrium and should not be the rate-limiting step.



Finally, it is noteworthy that Cu carbene such as **B** in Scheme 2 is electrophilic in character. Similar to the corresponding Rh(II) carbene, Cu carbene C−H insertion is sensitive to the electronic density of the targeted C−H bond.[17] From the acidity of the C−H bond of the aromatic heterocycles concerned in this investigation, the direct carbene insertion is expected to be difficult to occur due to low electronic density of the C−H bond. As far as we know, metal carbene C−H insertion into the 2-C of oxzoles or thiazoles is not known in the literature. On the contrary, the heterocycle-copper species has been generally suggested as the intermediate in the Cu-catalyzed C−H functionalization reaction of heteroaromatic compounds under basic conditions.[5] Summarizing all the information, we consider the reaction mechanism shown in Scheme 1 is more probable, while the Cu carbene direct C−H bond insertion as shown in Scheme 2 seems less likely. However, further study is needed to unambiguously establish the reaction mechanism.

In conclusion, we have developed an efficient Cu-catalyzed cross-coupling of azoles with *N*-tosylhydrazones through direct C−H bond functionalization, affording the corresponding benzylated aromatic heterocycles in moderate to good yields. This reaction provides an efficient access toward C−H bond functionalization by secondary benzyl group, which is difficult to achieve

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with other transition-metal-catalyzed direct C−H bond functionalization methods.

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author
wangjb@pku.edu.cn

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