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Formal Carbene C−H Bond Insertion in the Cu(I)-Catalyzed Reaction of Bis(trimethylsilyl)diazomethane with Benzoxazoles and Oxazoles

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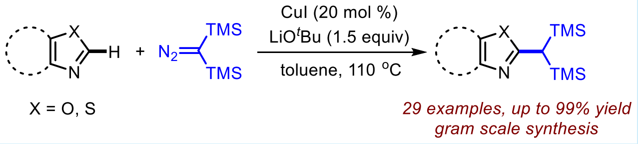
Supporting Information

ABSTRACT: A Cu(I)-catalyzed cross-coupling reaction of bis(trimethylsilyl)diazomethane and benzoxazoles/oxazoles is reported. A wide range of functional groups can be tolerated in this transformation. This reaction provides a new method to directly introduce a 1,1-bis(trimethylsilyl)methyl group into heteroaromatic C−H bonds. Subsequent transformations of 1,1-bis(trimethylsilyl)-methylated heteroaromatic compounds are also presented.

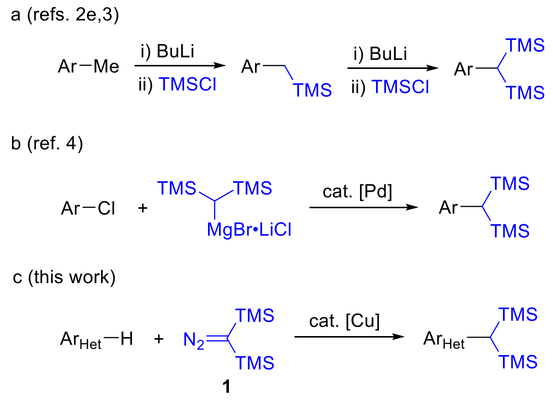


29 examples, up to 99% yield
gram scale synthesis

Organosilicon compounds play an important part in organic chemistry owing to their wide applications in organic synthesis.[1] Geminal disilyl compounds represent a special type of organosilicon compounds because of their unique structure and reactivity.[2] For example, geminal disilyl compounds can react as bicarbanion precursors and take part in the construction of C═C bonds in Peterson reactions[2b−e] and other functional group transformations.[2c,f] In addition, geminal disilyl compounds can also undergo reactions with only one of the two silyl groups, with the other one remaining in the products.[2g−k]

Traditional synthesis of the *gem*-disilyl unit requires stepwise deprotonative silylation under strong basic conditions (Scheme 1a).[2e,3] In recent years, several transition-metal-catalyzed processes were developed for the synthesis of these compounds, including Kumada cross-coupling reactions (Scheme 1b),[4] carbene insertion reactions of Si−H and Si−Si bonds,[5,6] hydrosilylation of unsaturated bonds,[7] and rearrangement reactions.[8] However, the methods to synthesize geminal disilyl compounds are still limited, and most of the known methods require introduction of two silyl groups in more than one step. To the best of our knowledge, the method for the direct introduction of a *gem*-disilyl unit into aromatic C−H bonds has not been explored.

Scheme 1. Synthesis of *gem*-Disilyl Compounds



On the other hand, transition-metal-catalyzed cross-coupling reactions of metal carbene precursors have recently emerged as a powerful tool for the construction of C−C and C−X bonds.[9,10] In this context, we have previously developed an efficient method for the direct heteroaromatic C−H functionalization through Cu(I)-catalyzed reaction of heteroaromatic compounds and *N*-tosylhydrazones.[10a] To further expand this type of Cu(I) carbene migratory insertion process, we have conceived using bis(trimethylsilyl)diazomethane **1** to access bis(trimethylsilyl)-methylated heteroaromatic compounds (Scheme 1c). Bis(trimethylsilyl)diazomethane **1** was synthesized previously by Barton and Hoekman.[11] However, it shows higher stability and different reactivity compared with that of other diazo compounds, such as (trimethylsilyl)diazomethane (TMSCHN$_2$), and the synthetic applications of this compound have not been explored until very recently.[12,13] Herein, we demonstrate that bis(trimethylsilyl)diazomethane undergoes efficient coupling with heteroarenes in the presence of a Cu(I) catalyst, affording the corresponding bis(trimethylsilyl)-methylated heteroaromatic compounds in moderate to good yields.

In the initial investigation, we examined the reactivity of various Cu(I) catalysts by using 5-methylbenzoxazole **2a** as the model substrate (Table 1, entries 1−3). The desired product **3a** was isolated in 21% yield with CuI as the catalyst and dioxane as the solvent at 110 °C (entry 1). When the ratio of **1** and **2a** was changed to 2:1, the yield of **3a** could be increased to 71% (entry 4). The reaction temperature was found to have a notable effect on the reaction. Reactions at 100 and 120 °C led to diminished yields (entries 5 and 6). By further screening the solvents, it was

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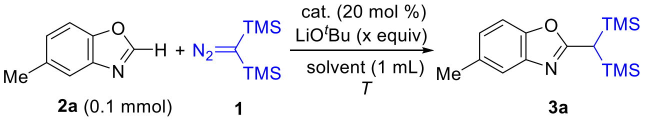
Table 1. Optimization of the Reaction Conditions[a]



entry[b]	ratio (1/2a)	cat. (mol %)	solvent	LiO^{t}Bu (x equiv)	T (°C)	yield (%)[c]
1	1:1	CuI (20)	dioxane	1	110	21
2	1:1	CuCl (20)	dioxane	1	110	trace
3	1:1	CuBr (20)	dioxane	1	110	20
4	2:1	CuI (20)	dioxane	1	110	71
5	2:1	CuI (20)	dioxane	1	100	40
6	2:1	CuI (20)	dioxane	1	120	43
7	2:1	CuI (20)	toluene	1	110	75
8	2:1	CuI (20)	toluene	1.5	110	85
9	2:1	CuI (20)	toluene	1.8	110	84
10[c]	2:1	CuI (20)	toluene	1.5	110	89
11[c]	2:1	CuI (20)	toluene	0	110	0
12[c]	2:1	$Rh_2(OAc)_4$ (1)	toluene	0	110	0
13[c]	2:1	$Pd(OAc)_2$ (5)	toluene	1.5	110	0
14[c]	2:1	$CuBr_2$ (20)	toluene	1.5	110	17

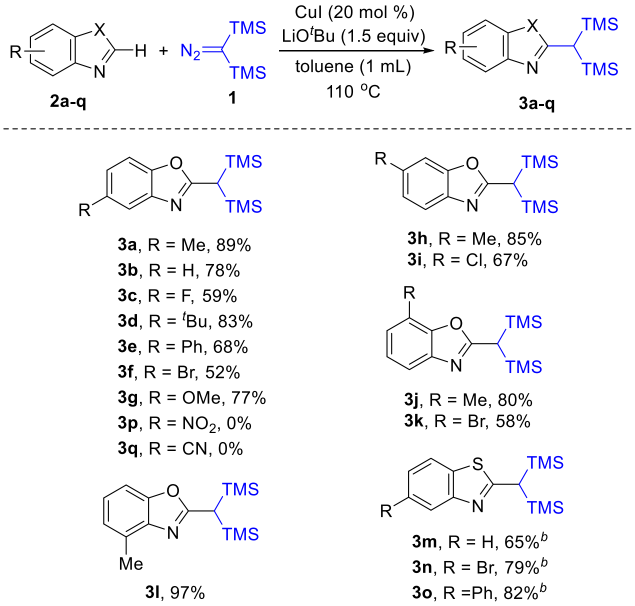
[a] Reaction conditions: bis(trimethylsilyl)diazomethane **1** (0.1 mmol), **2a** (0.1 mmol), CuI (0.02 mmol), LiO^{t}Bu (0.1 mmol), solvent (1.0 mL) for 8 h. [b] Isolated yield. [c] The reaction was carried out at 0.2 mmol scale.

proven that the reaction with toluene afforded the optimal result (entry 7). The choice of base also had a great influence on the reaction. Several organic and inorganic bases were tested, and the use of LiO^{t}Bu gave the best result (see Supporting Information). The yield of **3a** could be increased to 85% when the loading of base was increased to 1.5 equiv, but a further increase of the base loading had no obvious benefit (entries 8 and 9). Finally, under the optimized conditions, the reaction at the 0.2 mmol scale afforded the desired product in 89% isolated yield. Several control experiments were also carried out (entries 11−14). No desired product was observed without the addition of base. The reaction with Rh(II) and Pd(II) catalysts did not give product **3a** (entries 12 and 13), whereas the reaction with 20 mol % of $CuBr_2$ afforded **3a** in 17% yield (entry 14).

With the optimized conditions in hand, we then explored the substrate scope of this reaction (Scheme 2). For benzoxazoles, both electron-donating and electron-withdrawing group, including alkyl (**3a**, **3d**, **3h**, **3j**, **3l**), halogen (**3c**, **3f**, **3i**, **3k**), methoxyl (**3g**), and phenyl (**3e**), were well-tolerated and gave the corresponding products in moderate to good yields. However, substrates with a strong electron-withdrawing group failed to afford the corresponding products under standard conditions (**3p**, **3q**). Substituent groups at different positions showed similar reactivity (**3a** and **3h**, **3f** and **3k**). We also tested the reactivity of benzothiazole derivatives for this reaction, and the corresponding products can be obtained in moderate to good yields under modified conditions (**3m**−**o**).

We then expanded the substrate scope of the substituted oxazoles (Scheme 3). For 5-aryl-substituted oxazoles, both electron-donating and electron-withdrawing groups on the 5-aryl moiety were well-tolerated (**5a**−**h**). In addition to the substituted aryl group on the 5-position, naphthyl, furyl, and thienyl groups were also tolerated (**5l**−**n**). However, 5-pyridyl oxazole did not work for this reaction (**5o**). We also examined the reactivity of several 4-substituted oxazoles and obtained similar results as the corresponding 5-substituted substrates (**5i**−**k**). To our disappointment, the alkyl-substituted oxazole did not work for this transformation (**5p**).

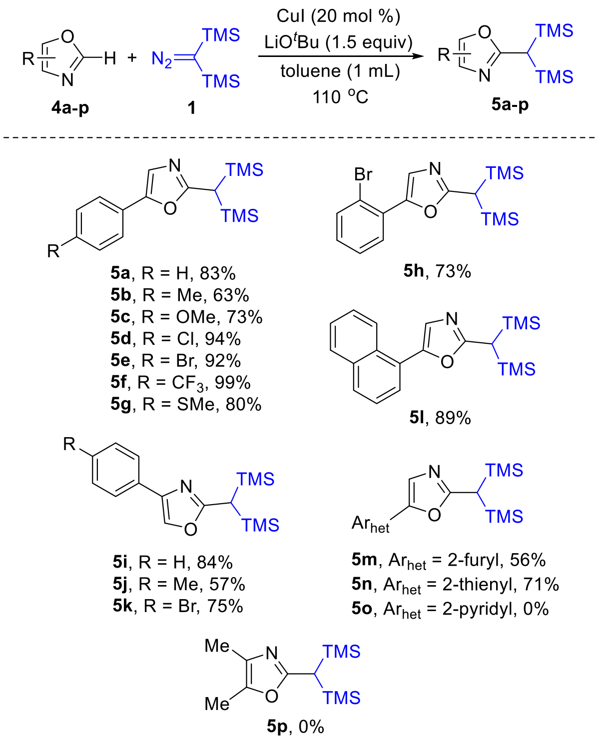
Scheme 2. Substrate Scope of Benzoxazoles and Benzothiazoles[a]



[a] Reaction conditions: bis(trimethylsilyl)diazomethane **1** (0.4 mmol), **2a**−**o** (0.2 mmol), CuI (0.04 mmol), LiO^{t}Bu (0.3 mmol), toluene (1.0 mL), 110 °C for 8 h. [b] 120 °C, LiO^{t}Bu (0.4 mmol). All yields refer to the isolated products.

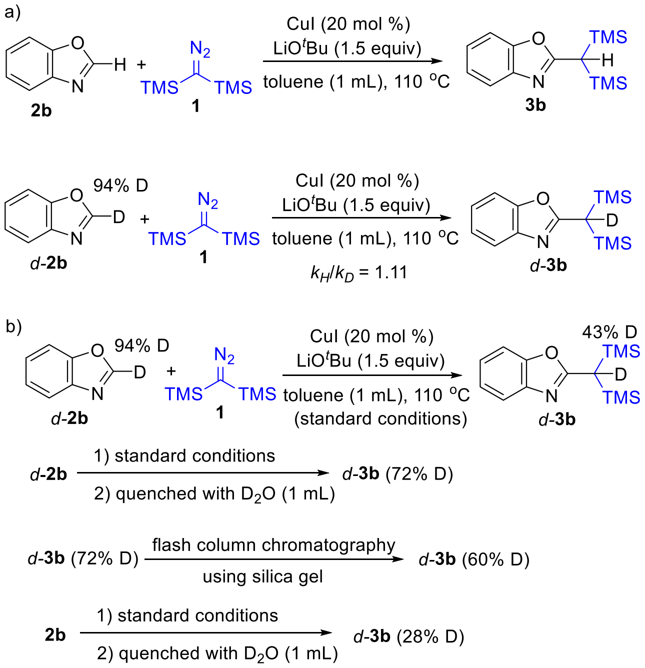
To gain further insight into the mechanism of this reaction, we have carried out kinetic isotope effects (KIE) and deuterium labeling experiments (Scheme 4). The result showed that the reaction had a delay time of about 5 min, and no significant primary kinetic isotope effects were observed in parallel kinetic experiments (Scheme 4a), which indicated that the deprotonation process should not be involved in the rate-limiting step. When the reaction was carried out with isotopically labeled substrate *d*-**2b**, obvious H/D exchange was observed (Scheme 4b). Quenching the reaction with D_2O led to a slight decrease of

Scheme 3. Substrate Scope of Oxazoles[a]



[a]Reaction conditions: bis(trimethylsilyl)diazomethane **1** (0.4 mmol), **4a–p** (0.2 mmol), CuI (0.04 mmol), LiO^{t}Bu (0.3 mmol), toluene (1.0 mL), 110 °C for 8 h. All yields refer to the isolated products.

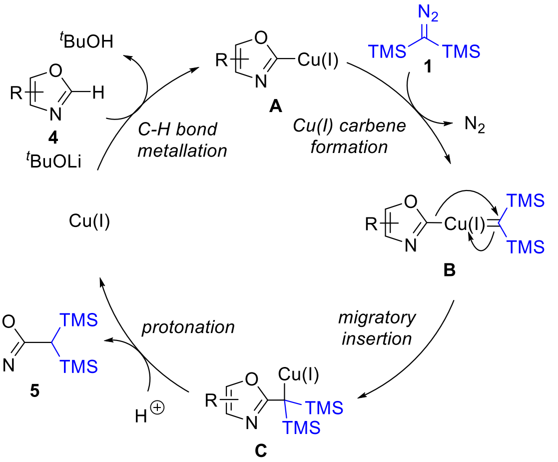
Scheme 4. KIE and Deuterium Labeling Experiments



the loss of deuterium in the product. Further treatment of deuterium-labeled *d*-**3b** with silica gel also led to the decrease of deuterium-labeled ratio. The loss of deuterium may be the result of the weak acidity of the geminal disilyl product. When the reaction of non-deuterium-labeled substrate **2b** was quenched with D_2O, the product was partially deuterium-labeled, which indicated that the product **3b** was partially deprotonated in the reaction mixture. This result also suggested the substantial high acidity of **3b**/*d*-**3b**.

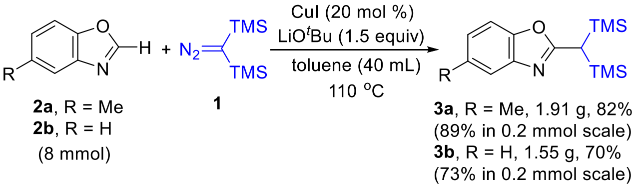
It has been reasoned that the current reaction does not follow the mechanism of classic carbene C−H bond insertion[14] for the following reasons: (1) in the absence of base, no formal insertion product was formed (Table 1, entry 11); (2) carbene insertion did not occur in the presence of Rh(II) catalyst (Table 1, entry 12); (3) the target C−H bond of benzoxazole or oxazole is electron-deficient, which is typically less reactive in classic carbene C−H insertions. Thus, based on the experimental results and our previous report,[10] a mechanistic rationale is proposed in Scheme 5. The reaction is initiated by the deprotonation of the relatively acidic C−H bond of the oxazole substrate **4** with LiO^{t}Bu, which is followed by transmetalation to the Cu(I) catalyst to generate oxazolyl Cu(I) species **A**. Intermediate **A** then reacts with the diazo substrate **1** to form a Cu(I) carbene species **B**. Subsequently, migratory insertion occurs to give Cu(I) intermediate **C**, followed by protonation to give the *gem*-disilylated product **5** and regenerate the Cu(I) catalyst.

Scheme 5. Proposed Reaction Mechanism



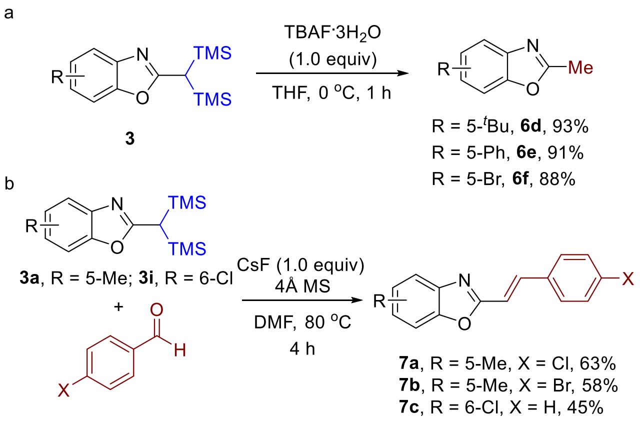
To demonstrate the practical application of this method, the Cu(I)-catalyzed cross-coupling reaction was carried out at gram scale (Scheme 6). The corresponding geminal disilyl compounds **3a** and **3b** could be successfully obtained, albeit in slightly diminished yields.

Scheme 6. Gram-Scale Synthesis



Furthermore, to explore the synthetic application of the geminal disilyl compounds obtained from the Cu(I)-catalyzed cross-coupling reaction of bis(trimethylsilyl)diazomethane and benzoxazoles, we have attempted further transformations of these compounds (Scheme 7). The geminal disilyl compounds (**3d, 3e, 3f**) could be easily transformed into the corresponding methylated products (**6d, 6e, 6f**) under mild conditions (Scheme 7a).[15] Finally, the geminal disilyl compounds **3a** and

Scheme 7. Transformations of the *gem*-Disilylated Products



3i could smoothly undergo Peterson reaction and give the corresponding olefination products in moderate yields (Scheme 7b).

In summary, we have developed a Cu(I)-catalyzed cross-coupling of bis(trimethylsilyl)diazomethane and benzoxazoles/oxazoles via a metal carbene migratory insertion process. This reaction provides a new method to directly introduce 1,1-bis(trimethylsilyl)methyl group into heteroaromatic C−H bonds. By using this cross-coupling reaction, a series of 1,1-bis(trimethylsilyl)-methylated heteroaromatic compounds have been successfully synthesized in moderate to good yields from easily available materials. The reaction uses readily available and inexpensive CuI as the catalyst and tolerates a wide range of functional groups. We thus expect this bis(trimethylsilyl)-methylation method to be a convenient way to synthesize geminal disilyl compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00391.

Experiment details, spectra data, and copies of ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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