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CuCl-Catalyzed Direct C-H Alkenylation of Benzoxazoles with Allyl Halides

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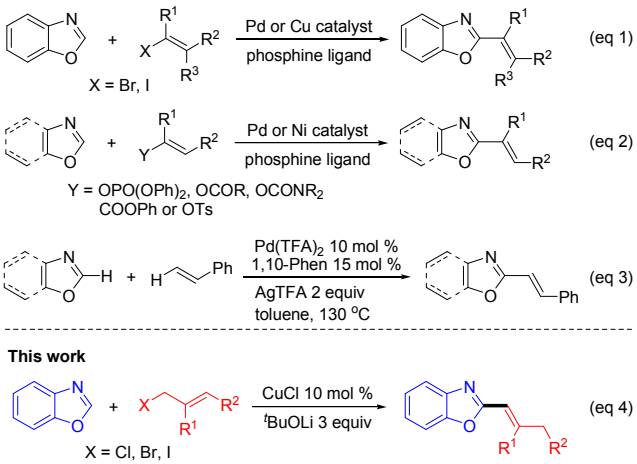
An efficient and concise CuCl-catalyzed C2-alkenylation reaction of benzoxazoles with allyl halides has been established. The distinctive features of this protocol include the use of an inexpensive copper salt as catalyst, simple and readily available starting materials, and ligand-free conditions. An important application of this method to the synthesis of 1,3-diene substituted benzoxazoles has also been achieved.

Benzoxazole derivatives are important aromatic heterocycles which exist in many natural products, agrochemicals as well as biologically and pharmaceutically active molecules.[1] They are also widely used in numerous organic functional materials such as liquid crystals and fluorescent materials.[2] Therefore, much effort has been devoted to developing efficient synthetic methods for synthesizing this type of aromatic heterocycles, especially those with an alkenyl substituent at C-2 position.[3,4] Among these, transition-metal-catalyzed C-H functionalizations of heterocycles have been demonstrated to be the powerful tools to access C2-alkenylbenzoxazoles.[4] In this context, many catalytic approaches using C–X/C–H direct alkenylation strategies from benzoxazoles with various electrophilic coupling partners have been developed. For instance, the groups of Doucet, Piguel and others have independently reported several efficient alkenylation reactions of oxazole derivatives employing alkenyl halides as coupling partners (Scheme 1, eq 1).[4a-f] In addition to alkenyl halides, alkenyl phosphates and tosylates as well as enol and unsaturated esters derivatives were successfully demonstrated as the alternative coupling partners for these C–X/C–H direct alkenylations by Ackermann, Kwong, and Itami (Scheme 1, eq 2).[4g-i] However, the use of above mentioned poorly available alkenyl reagents has restricted applications of these reactions. In 2014, an alternative and more straightforward palladium-catalyzed cross-dehydrogenative coupling of benzoxazoles with a vinyl moiety without using prefunctionalized substrates to provide C2-alkenylated benzoxazoles was successfully achieved by Ong and co-workers (Scheme 1, eq 3).[5]

On the other hand, allyl halides are easily available and have been used in a wide range of allylation reactions.[6] However, the reports for efficient and selective alkenylations of heteroarenes using allyl halides as the alkenyl reagents are quite limited.[7] Very recently, Chang and co-workers discovered a [Cu(NHC)]-catalyzed C-H allylation/isomerization process to access both electron-deficient and electron-rich alkenylated (hetero)arenes by using allyl halides as the reactants for the first time.[8] As a continuation of our interest in the synthesis and transformations of heterocycles,[9] herein we report a convenient method for C2-alkenylbenzoxazoles synthesis based on CuCl-catalyzed direct alkenylation reaction of benzoxazoles with allyl halides (Scheme 1, eq 4). The distinctive features of this new protocol include the use of inexpensive copper salt as catalyst, simple and readily available starting materials, and ligand-free conditions. An important application of this method to the synthesis of 1,3-diene substituted benzoxazoles using 1,4-dibromobut-2-ene as the reactant was also demonstrated.



Scheme 1. Direct C2-alkenylation of benzoxazoles

The reaction was initially optimized using benzoxazole **1a** and allyl bromide **2a** as model substrates (Table 1). Gratifyingly, when **1a** and **2a** were mixed with $Cu(OTf)_2$ in the presence of ^tBuOLi in

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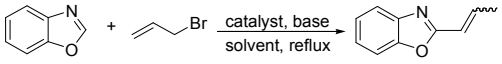
toluene at reflux temperature for 2 hours, the reaction afforded the C2-alkenylbenzoxazole **3a** in 40% isolated yield (entry 1). Encouraged by this initial result, the effect of catalysts was subsequently investigated. Among the copper sources used, $Cu(OAc)_2$ and $Cu(acac)_2$ were found to be less efficient (entries 2 and 3). Interestingly, when CuCl was employed as the catalyst in this coupling reaction, **3a** could be obtained in 65% yield, whereas a low yield of **3a** was obtained when the reaction was catalyzed by CuI or CuBr (entries 4-6). Two palladium catalysts, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$, were examined under the similar reaction conditions and only trace of product **3a** was detected by TLC (entries 7 and 8). Subsequently, a range of inorganic as well as organic bases were examined for this reaction (entries 9–11), and only ^{t}BuOLi proved competent. A rapid solvent screening revealed that the reaction was sluggish in CH_2Cl_2, but gave moderate yields of **3a** in other solvents such as CH_3CN, THF and dioxane (entries 12–15). Predictably, when the reaction was carried out under a N_2 atmosphere, the highest yield of the product was obtained (entry 16). For comparison, the reaction was performed in the absence of a catalyst, but no reaction occurred under such conditions (entry 17). Finally, the conditions in entry 16 (Table 1) were identified as the optimal conditions.

After establishing standard reaction conditions, the scope of this direct C2-alkenylation was investigated by using a series of benzoxazoles and allyl bromide derivatives. As illustrated in Table 2, excellent product yield (90%) was obtained when methallyl bromide **2b** was employed in this novel coupling reaction under the optimized reaction conditions (**3b**). Next, several substituted benzoxazoles have been subjected to the alkenylation conditions, and generally high yields were obtained. For example, benzoxazoles bearing methyl or halide groups on the 5, 6 or 7-position of the

Table 1. Optimization of reaction conditions[a]

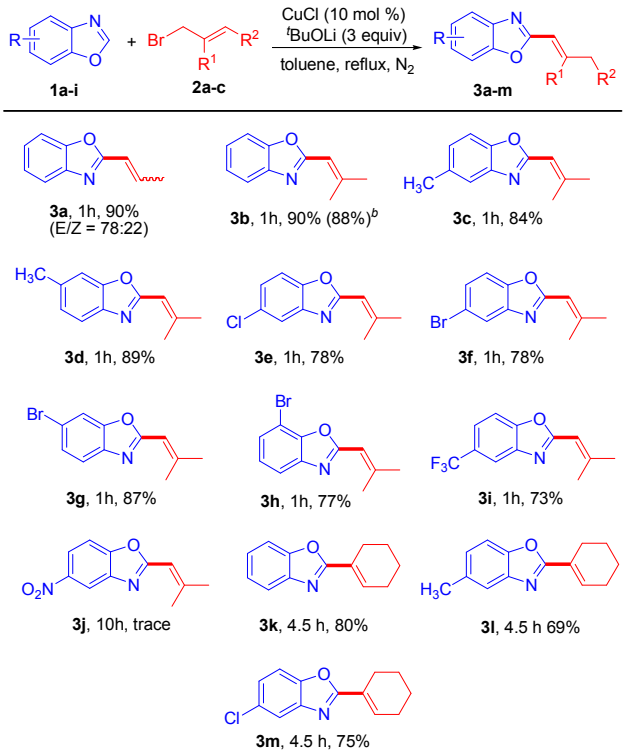


1a **2a** **3a**

entry	cat. (10 mol%)	base (3 equiv)	solvent	time (h)	yield (%)[b]
1	$Cu(OTf)_2$	^{t}BuOLi	toluene	2	40 (42)[c]
2	$Cu(OAc)_2$	^{t}BuOLi	toluene	2	30 (30)[c]
3	$Cu(acac)_2$	^{t}BuOLi	toluene	3	29 (33)[c]
4	CuCl	^{t}BuOLi	toluene	1	65
5	CuBr	^{t}BuOLi	toluene	2	20 (30)[c]
6	CuI	^{t}BuOLi	toluene	2	30 (36)[c]
7	$Pd(PPh_3)_4$	^{t}BuOLi	toluene	9	trace
8	$Pd_2(dba)_3$	^{t}BuOLi	toluene	13	trace
9	CuCl	NaOH	toluene	24	0
10	CuCl	Cs_2CO_3	toluene	24	0
11	CuCl	DBU	toluene	24	0
12	CuCl	^{t}BuOLi	CH_2Cl_2	4	5
13	CuCl	^{t}BuOLi	CH_3CN	4	46
14	CuCl	^{t}BuOLi	THF	1	40
15	CuCl	^{t}BuOLi	dioxane	4	30
16[c]	CuCl	^{t}BuOLi	toluene	1	90
17	---	^{t}BuOLi	toluene	10	0

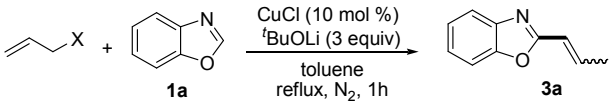
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), base (3.0 mmol) and catalyst (0.1 mmol) in 3.0 mL of solvent at reflux temperature. [b] Yield of isolated product after chromatography. [c] The reaction was proceeded under N_2 atmosphere.

Table 2 Scope of substituted benzoxazoles and allyl bromide derivatives[a]



[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), ^{t}BuOLi (3.0 mmol) and CuCl (0.1 mmol) in 3.0 mL of toluene at reflux temperature under N_2 atmosphere and isolated yields were reported. [b] The reaction was performed on a 1.2 g scale of benzoxazole.

phenyl rings gave the corresponding products (**3c-h**) in good yields. Moreover, the reaction also proceeded smoothly with a trifluoromethyl containing substrate, affording the corresponding product **3i** in 73% yield. However, substrate containing a nitro group on the 5-position of the benzoxazole ring (**3j**) did not yield any desired alkenylated product. Notably, when 3-bromocyclohex-1-ene **2c** was subjected to this transformation as the substrate, the reaction also proceeded well and afforded the corresponding products in good yields with various benzoxazoles (**3k–m**). Finally, we also demonstrated the potential of scaling up this novel alkenylation; the reaction of **1a** and **2b** was run on a 1.2 g scale under standard conditions for 2 hours, providing **3b** in 88% isolated yield.



4, X = Cl — 56% (*E*/*Z* = 64:36) from **4**
5, X = I — 91% (*E*/*Z* = 1:1) from **5**
2a, X = Br — 90% (*E*/*Z* = 78:22) from **2a**

Scheme 2. The reaction of allyl chloride **4** and allyl iodide **5** with benzoxazole **1a**

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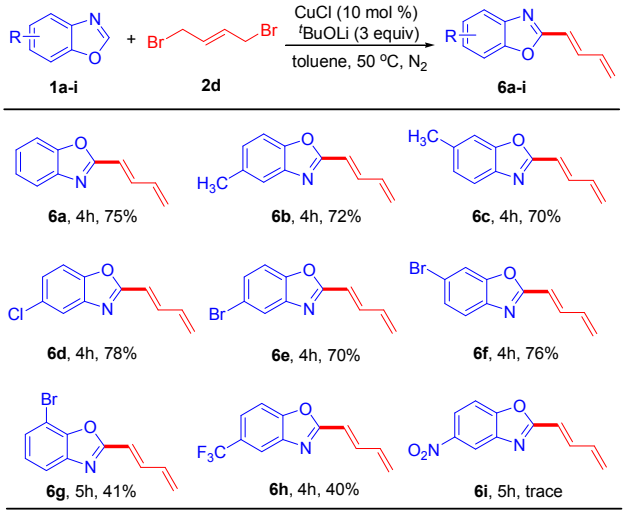
Moreover, it should be mentioned that the same C2-alkenylbenzoxazole product **3a** can be obtained in 56% and 91% isolated yield respectively, under the identical conditions from the reaction of allyl chloride **5** or allyl iodide **6** with benzoxazole **1a**, albeit with low diastereoselectivities (Scheme 2).

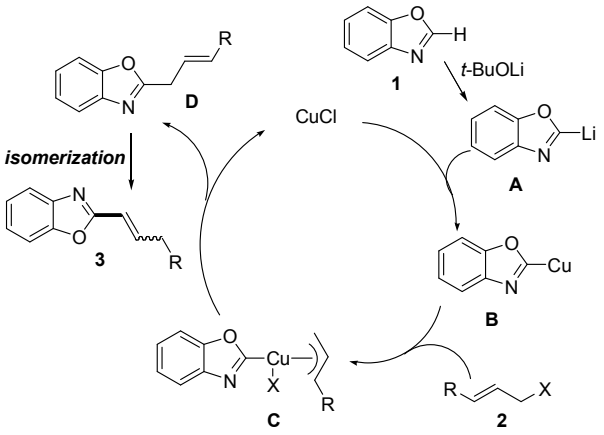
Table 3. Synthesis of 1,3-diene containing benzoxazoles.[a]



[a] Reaction conditions: **1** (1.5 mmol), **2d** (1.0 mmol), ^{t}BuOLi (3.0 mmol) and CuCl (0.1 mmol) in 3.0 mL of toluene at 50 °C under N_2 atmosphere and isolated yields were reported.

Finally, this coupling reaction was successfully applied to the synthesis of benzoxazole containing 1,3-butadiene derivatives. Integration of a 1,3-butadiene moiety into heteroarenes is synthetically valuable because both of them are all widely utilized in polymer and materials chemistry. However, the synthetic methods to access such type of compounds are very limited.[10]

We found that under slightly modified reaction conditions, the CuCl-catalyzed coupling of benzoxazole with 1,4-dibromobut-2-ene led to the formation of 2-(buta-1,3-dienyl)benzo[*d*]oxazole in 75% yield (**6a**). Subsequently investigation indicated that various substituents on the aromatic ring were all compatible with the present catalytic system and afforded the desired 2-(1,3-diene) substituted benzoxazoles in moderate to good yields (**6b–h**). However, just as the result in Table **2**, a nitro substituted benzoxazole was also failed in this transformation (**6i**).



Scheme 3. Proposed mechanism of the reaction

On the basis of the above results and related literature,[8, 11] a plausible mechanism is proposed as shown in Scheme 3. First, the deprotonation of benzoxazole on C2-position occurred in the presence of ^{t}BuOLi, resulting in the formation of intermediate **A**, which react with Cu(I) catalyst to form a copper-aryl intermediate **B**. Subsequently, an oxidative insertion of allyl halides into intermediate **B** take place to produce an π-allyl Cu^{III} complex intermediate **C**. Next, reductive elimination of the intermediate **C** affords the allylated intermediate **D** with the regeneration of catalyst. Finally, fast isomerization of intermediate **D** delivers the alkenyl product **3**.

In conclusion, we have developed an efficient and concise CuCl-catalyzed C2-alkenylation reaction of benzoxazoles with allyl halides. Furthermore, this method has been successfully applied in the synthesis of 1,3-diene substituted benzoxazoles using 1,4-dibromobut-2-ene as the reactant. The distinctive features of this new protocol include the use of inexpensive copper salt as catalyst, simple and readily available starting materials as well as ligand-free conditions.

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