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One-pot synthesis of benzofused heteroaryl azoles *via* tandem C-heteroatom coupling/C–H activation of azoles†

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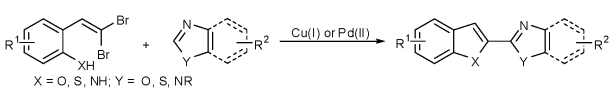
The Cu(I) or Pd(II)-catalyzed cross-couplings of *gem*-dihaloolefins with azoles *via* tandem C-heteroatom coupling/C–H activation for the preparation of benzofused heteroaryl azoles have been developed.

Benzofuranyl, benzothiophenyl and indolyl azoles are a class of privileged biheteroaryl structural motifs in bioactive natural products, pharmaceuticals (*e.g.*, anxiety inhibitor, and tumor antagonist),[1] and organic functional materials.[2] The conventional methods to forge these heteroaryl azoles mainly involve intermolecular condensations of heteroaryl carboxylic acids or aldehydes with *o*-aminophenols, benzene-*o*-diamines or *o*-aminobenzenethiols.[3] The transition metal-catalyzed coupling reactions of azoles with heteroarenes also represents one of the effective methodologies for the preparation of these biheteroaryl units. However, such heteroaryl-heteroaryl bond-forming examples are sporadic in both of traditional Ar–X/Ar–M couplings[4] and direct C–H bond functionalization.[5] Despite remarkable advances in these types of transformations, from academic and practical standpoints, development of reliable alternatives for the straightforward synthesis of these benzofused heteroaryl azoles, especially starting from other readily available sources, is still very attractive to synthetic and medicinal chemists.

The *gem*-dihalovinyl compounds as versatile partners have attracted considerable interests in transition metal-catalyzed cross-coupling chemistry owing to higher reactivity, and ready availability from inexpensive aldehydes. Recently, a variety of novel and elegant methods have been developed to allow the Pd and/or Cu-catalyzed cross-couplings of *gem*-dihaloolefins with various organometallic nucleophiles, nitrogen nucleophiles or dialkyl phosphites to form functionalized alkynes,[6] dienes,[7] heterocycles[8] or carbocycles.[9] Quite recently, Piguel and co-workers described the first use of 1,1-dibromo-1-alkenes in the intermolecular cross-coupling of azoles *via* the direct functionalization of C–H bonds, providing an efficient route to diverse alkynyl azoles.[10] Despite remarkable interest in employing the *gem*-dihalovinyl substrates to achieve polycyclic heteroaromatics *via* metal-catalyzed tandem amination or Suzuki–Miyaura coupling/intramolecular C–H activation,[11] to our knowledge the tandem processes *via* an intermolecular C–H functionalization to form biheteroaryl units have not yet been explored. Herein, we disclose an effective domino Cu(I) or Pd(II)-catalyzed Ullmann-type C-heteroatom coupling of *gem*-dihaloolefins/C–H activation of azoles to create various benzofused heteroaryl azoles (Scheme 1). This sequential strategy could offer a straightforward and highly efficient alternative to access benzofuranyl, benzothiophenyl and indolyl azoles, and avoid tedious separation and purification of intermediate products.

Inspired by our previous study on copper-catalyzed direct arylation of heteroaromatic C–H bonds,[12] we initially focused on copper-catalytic systems due to economic attractiveness and good functional tolerance. Our investigation started with the coupling of 2-*gem*-dibromovinylphenol **1a** and benzothiazole **2a** in the presence of CuI and Phen (1,10-phenanthroline) using K_3PO_4 as the base in 1,4-dioxane for 24 h at 120 °C. To our delight, the biheteroaryl product **3a** was obtained in 55% yield (Table 1, entry 1). Subsequently, we examined several bases (*i.e.*, *t*-BuOK, Cs_2CO_3, K_3PO_4/NEt_3, and *t*-BuOLi). *t*-BuOLi proved to be the most efficient whereas the more strongly basic *t*-BuOK only provided 28% yield of **3a** (Table 1, entries 2–5). After screening a series of ligands (*e.g.*, Phen, DMEDA (*N*,*N*′-dimethylethylenediamine), PPh_3, and L-proline), Phen turned out to be the best choice (Table 1, entries 5–9). Among solvents investigated, 1,4-dioxane was clearly a more efficient solvent (Table 1, entries 5, 10–11). Other sources of the copper salt were inferior to CuI (Table 1, entries 5, 12–13). In addition, prolonging reaction time, elevating reaction temperature, and increasing CuI loading could significantly improve yields (Table 1, entries 14–15). Thus, the best result was obtained in 1,4-dioxane at 140 °C for 30 h using *t*-BuOLi as the base in the presence of a catalyst system that was generated *in situ* from CuI (20 mol%) and Phen (20 mol%).



Scheme 1 Tandem C-heteroatom coupling/C–H activation of azoles.

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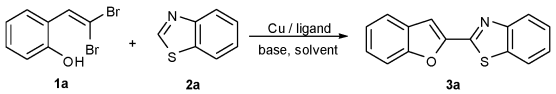
Table 1 Optimization of the coupling of 2-*gem*-dibromovinylphenol with benzothiazole[a]



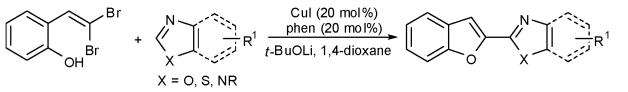
Entry	Cu source	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	Phen	K_3PO_4	1,4-dioxane	55
2	CuI	Phen	*t*-BuOK	1,4-dioxane	28
3	CuI	Phen	Cs_2CO_3	1,4-dioxane	trace
4	CuI	Phen	K_3PO_4/NEt_3	1,4-dioxane	16[c]
5	CuI	Phen	*t*-BuOLi	1,4-dioxane	64
6	CuI	—	*t*-BuOLi	1,4-dioxane	14
7	CuI	PPh_3	*t*-BuOLi	1,4-dioxane	25
8	CuI	L-proline	*t*-BuOLi	1,4-dioxane	36
9	CuI	DMEDA	*t*-BuOLi	1,4-dioxane	29
10	CuI	Phen	*t*-BuOLi	toluene	20
11	CuI	Phen	*t*-BuOLi	DMF	25
12	CuBr·SMe_2	Phen	*t*-BuOLi	1,4-dioxane	51
13	CuBr	Phen	*t*-BuOLi	1,4-dioxane	45
14	CuI	Phen	*t*-BuOLi	1,4-dioxane	75[d]
15	CuI	Phen	*t*-BuOLi	1,4-dioxane	83[e]

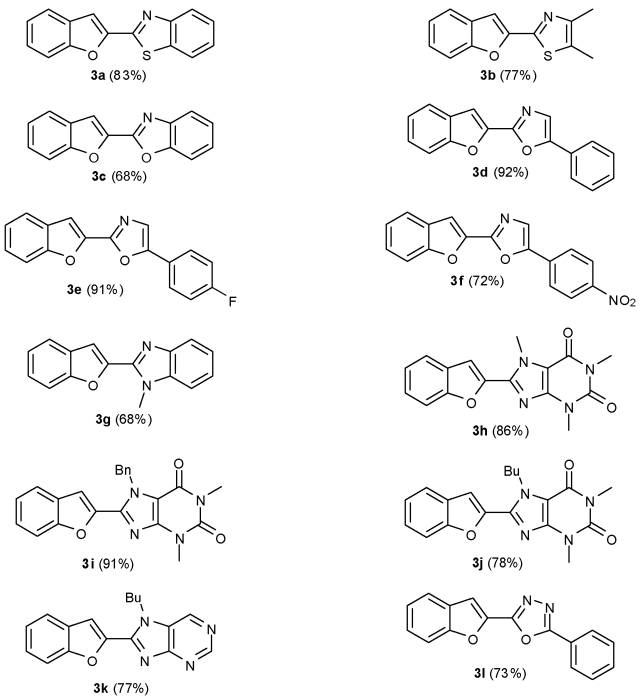
[a] Reactions were carried out using copper(I) salt (10 mol%), ligand (10 mol%), base (6 equiv), benzothiazole (0.25 mmol), and 2-*gem*-dibromovinylphenol (0.5 mmol) for 24 h at 120 °C. [b] Isolated yields. [c] K_3PO_4 (3 equiv), and NEt_3 (3 equiv). [d] 140 °C, 30 h. [e] CuI (20 mol%), and ligand (20 mol%) for 30 h at 140 °C.

With the optimized conditions now in hand, we tested their application to the one-pot synthesis of 2-(benzofuran-2-yl)-azoles **3a–l**. It was gratifying to find that a broad range of azoles reacted smoothly with 2-*gem*-dibromovinylphenol in good to excellent yields of desired products (Table 2). For example, thiazoles (*e.g.*, 4,5-dimethylthiazole, and benzothiazole) gave the corresponding 2-(benzofuran-2-yl)-thiazoles in good yields (Table 2, entries **3a–b**). The catalytic system could be also extended to an array of oxazoles (Table 2, entries **3c–f**). Notably, 2-(benzofuran-2-yl)-benzoxazole **3c**, which is a predominant chemical ingredient in sunscreens for the effective protection of skin from sun radiation, was synthesized in 68% yield.[13] Worthy of note was that the reaction condition was suitable for various imidazoles to furnish benzofuranyl imidazoles (Table 2, entries **3g–k**). For example, the coupling of 2-*gem*-dibromovinylphenol with xanthines afforded 8-benzofuranyl xanthines in good to excellent yields, which are important biologically active alkaloids and highly potent antagonists at human A_{2B} adenosine receptors (Table 2, entries **3h–j**).[1e] In addition, 2-phenyl-1,3,4-oxadiazole was also reactive (Table 2, entry **3l**).

To further expand the scope of our methodology, the tandem cross-couplings of other 2-*gem*-dibromovinylphenol derivatives were investigated as illustrated in Table 3. Overall, we were pleased with the generality of our protocol. A relatively wide arrange of 2-*gem*-dibromovinylphenols could be efficiently converted into the corresponding benzofuranyl azoles in synthetically useful yields (Table 3, **4a–h**). On the other hand, various azoles (*i.e.*, thiazoles, oxazoles, and imidazoles) were heteroarylated with 2-*gem*-dibromovinylphenols. To our delight, this synthetic strategy was also applicable for the synthesis of 2-(benzothiophen-2-yl)-azoles. Treatment of 2-*gem*-dibromovinylphenthiol with various azoles

Table 2 Synthesis of 2-(benzofuran-2-yl)-azoles[a,b]





[a] Reactions were carried out using CuI (20 mol%), Phen (20 mol%), *t*-BuOLi (6 equiv), azole (0.25 mmol), and 2-*gem*-dibromovinylphenol (0.5 mmol) for 30 h at 140 °C. [b] Isolated yields.

(*e.g.*, xanthine, 5-phenyloxazole, and 2-phenyl-1,3,4-oxadiazole) smoothly gave the corresponding 2-(benzothiophen-2-yl)-azoles under the optimized conditions (Table 3, **4i–k**).

While the coupling of 2-*gem*-dibromovinylphenols and 2-*gem*-dibromovinylphenthiols with various azoles proceeded well in the Cu(I)/Phen catalytic system, 2-*gem*-dibromovinylbenzenamine could not afford 2-(indole-2-yl)-azoles. However, the catalyst system generated *in situ* from $Pd(OAc)_2$/S-Phos/CuI and *t*-BuOLi gave 2-(indol-2-yl)-benzothiazole **4l** in 52% yield in toluene at 120 °C for 24 h (Scheme 2).

In summary, we have developed the Cu(I) or Pd(II)-catalyzed cross-coupling of *gem*-dihaloolefins with azoles *via* tandem C-heteroatom coupling/C–H activation for the preparation of benzofused heteroaryl azoles. Particularly noteworthy is that our strategy is not only suitable for various benzofused heterocycles (*e.g.*, benzofurans, benzothiophenes, and indole), but also a relatively wide range of azoles (*e.g.*, thiazoles, oxazoles, imidazoles, and oxadiazoles). The reaction conditions were also compatible with the presence of functional groups (*e.g.*, halides, nitro groups and methoxyl groups), which may then be subject to further synthetic transformations. Further studies aimed at elucidating the mechanism of the reactions, and at extending this catalytic method to other cross-coupling reactions are underway.

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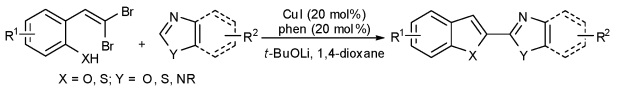
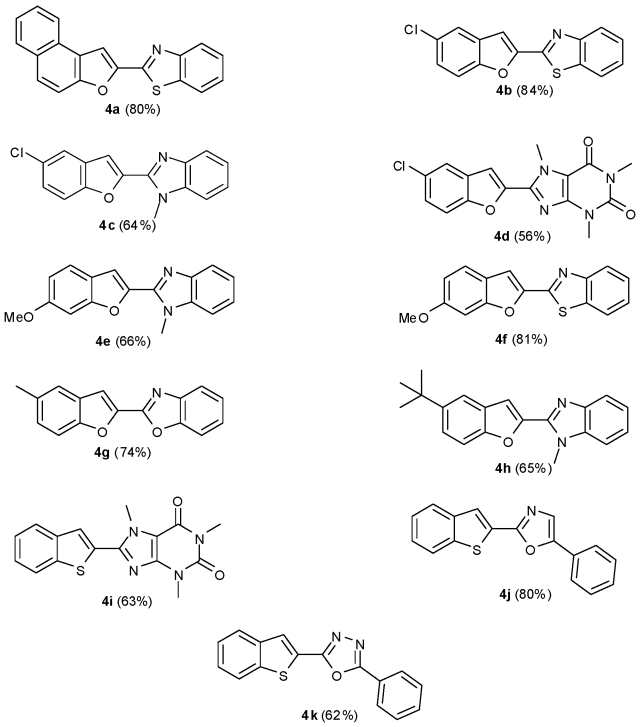
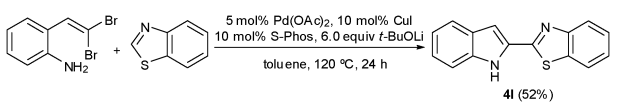
Table 3 Synthesis of 2-(benzofuran-2-yl)- or 2-(benzothiophen-2-yl)-azoles[a,b]





[a] Reactions were carried out using CuI (20 mol%), Phen (20 mol%), *t*-BuOLi (6 equiv), azole (0.25 mmol), and 2-*gem*-dibromovinylphenol or 2-*gem*-dibromovinylphenthiol (0.5 mmol) for 30 h at 140 °C. [b] Isolated yields.



Scheme 2 Synthesis of 2-(indol-2-yl)-benzothiazole **4l**.

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