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Copper-Catalyzed Dehydrogenative Cross-Coupling of Benzothiazoles with Thiazoles and Polyfluoroarene

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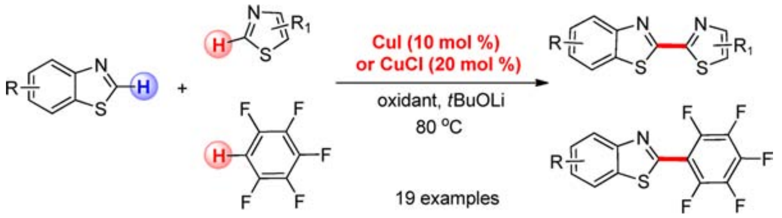
ABSTRACT



A copper-catalyzed dehydrogenative cross-coupling of benzothiazoles with thiazoles and polyfluoroarene under mild reaction conditions is described. This protocol provides a straightforward and operationally simple method for the synthesis of the 2,2′-linkage of thiazoles and 2-polyfluoroarylthiazoles of interest in life and material sciences.

As an attractive alternative to traditional cross-coupling in the construction of carbon−carbon (C−C) bonds, transition-metal-catalyzed direct functionalization of C−H bonds has gained considerable attention.[1] In particular, dehydrogenative cross-coupling from two simple C−H bonds represents the most efficient and straightforward access to the target molecules, since this tandem oxidation of C−H bonds avoids the prefunctionalization steps of both cross-coupling partners.[2] In recent years, impressive progress has been made in the formation of aryl−aryl bonds via this strategy.[3] However, in most of the cases, palladium catalysts have been used in conjunction with stoichiometric amounts of copper and silver reoxidants. Although these achievements are promising, new catalytic systems using less expensive and abundant metal catalysts, such as copper, to execute such C−H bond

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functionalization reactions are appealing. During the past few years, considerable effort has been devoted to using copper catalysis in the construction of C−heteroatom and C−C bonds through selective catalytic functionalization of aryl C−H bonds.[4] However, the copper-catalyzed dehydrogenative diaryl cross-coupling reaction remains a great challenge and largely unexplored. The reason is that this strategy is often difficult to realize, as both coupling partners, in particular coupling partners with similar structure and reactivity, are susceptible to oxidative homocoupling in the presence of copper salts.[5] To the best of our knowledge, rare examples have been reported in this challenging area so far.[6] Consequently, new copper-catalytic systems to overcome these challenges are highly desirable. In continuing our efforts in transition-metal-catalyzed dehydrogenative cross-couplings,[7] herein, we describe a copper-catalyzed dehydrogenative cross-coupling of benzothiazoles with thiazoles through dual C−H bond functionalization under mild reactions in a highly efficient manner and with excellent regioselectivity. Furthermore, the methodology could also be extended to polyfluoroarene.

In view of the importance of azoles,[8] in particular, bithiazaole derivatives, that are found in many biologically active compounds, natural products,[9] and materials (e.g., solar cells),[10] as well as the fact that no copper-catalyzed cross-coupling of both similar thiozoles has been reported due to difficulties in suppressing undesired homocouplings,[5] benzothiazole **1a** and 4,5-dimethylthiazole **2a** were chosen as model substrates. Initially, no desired product **3a** was observed, when **1a** (1.0 equiv) and **2a** (2.0 equiv) were treated with *t*BuOLi in DMF at 80 °C by using Ag_2CO_3 as an oxidant, $Cu(OAc)_2$ (20 mol %) as a catalyst, and 1,10-phenanthroline (phen) as a ligand (Table 1, entry 1). Further investigating the solvent effect, we found that nonpolar solvent toluene was the best reaction medium, providing **3a** in 35% yield (Table 1, entry 4). Encouraged by these preliminary results, we subsequently tried to optimize the reaction conditions by using different bases, copper salts, ligands, and oxidants. *t*BuONa, *t*BuOK, and $(t\mathrm{BuO})_2\mathrm{Mg}$ all failed to give **3a**; only *t*BuOLi is a suitable base. The choice of copper salts is also critical to the reaction efficiency; CuI proved to be the optimum catalyst with 60% isolated yield of **3a** obtained when 2,2′-bipydyl (bpy) was used as a ligand (Table 1, entry 6). Other oxidants such as AgOAc, $AgNO_3$, air, and O_2 showed less or no activity (Table 1, entries 8−11). Further improvement of the reaction efficiency by increasing the amount of **2a** to 3.0 equiv led to a higher yield (Table 1, entry 12). Interestingly, the absence of bpy also furnished **3a** in a comparable yield (Table 1, entry 13), whereas the absence of CuI or Ag_2CO_3 failed to give any desired product (Table 1, entries 14−15), thus implying that a copper redox catalytic cycle was involved in the reaction. Finally, the best yield of **3a** (71%) was afforded by decreasing the loading of CuI to 10 mol % (Table 1, entry 16).

With the optimum reaction conditions determined (Table 1, entry 16), various benzothiazoles and thiazoles were then investigated (Scheme 1). The mild reaction conditions allow for preparation of a variety of 2,2′-linkages of thiazoles in moderate to good yields. Different substituted benzothiazoles furnished the corresponding products smoothly (**3a**−**f**). Importantly, 5-(2-(benzyloxy)ethyl)-4-methylthiazole also tolerated reaction conditions, thus providing opportunities for further transformations (**3g**). It should be mentioned that excellent regioselectivity at the C-2 position of thiazoles was also observed when thiazole and 4-methylthiazole were investigated (**3h**−**i**),[11] which is in contrast to a previous reported method by which a diarylated product is normally obtained.[4c] Consequently, these resulting products **3h**−**i** could be further transformed by sequential C−H functionalization at the C4 position of the thiazole part,[12] thus featuring the utility of this protocol.

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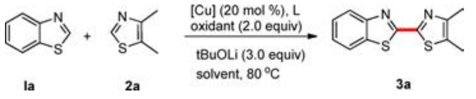
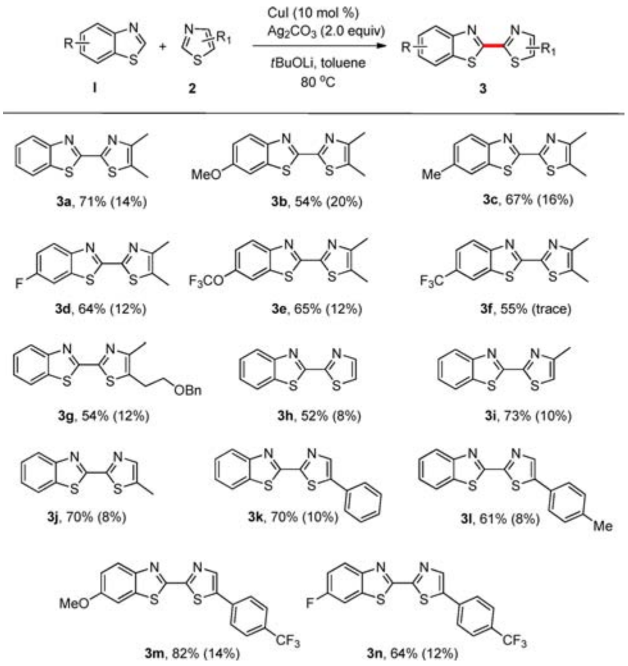
Table 1. Representative Results for Optimization of Cu-Catalyzed Dehydrogenative Cross-Coupling of Benzothiazole **1a** with 4,5-Dimethylthiazole **2a**[a]



entry	[Cu]	L	oxidant	solvent	yield [%][b]
1	$Cu(OAc)_2$	phen	Ag_2CO_3	DMF	trace
2	$Cu(OAc)_2$	phen	Ag_2CO_3	DMSO	trace
3	$Cu(OAc)_2$	phen	Ag_2CO_3	DME	21
4	$Cu(OAc)_2$	phen	Ag_2CO_3	toluene	35
5	CuI	phen	Ag_2CO_3	toluene	44
6	CuI	bpy	Ag_2CO_3	toluene	70(60)
7	CuI	bpy	Ag_2CO_3	toluene	72
8	CuI	bpy	AgOAc	toluene	65
9	CuI	bpy	$AgNO_3$	toluene	45
10	CuI	bpy	air	toluene	trace
11	CuI	bpy	O_2	toluene	trace
12[c]	CuI	bpy	Ag_2CO_3	toluene	(66)
13[c]	CuI	none	Ag_2CO_3	toluene	(68)
14[c]	none	none	Ag_2CO_3	toluene	NR
15[c]	CuI	none	none	toluene	NR
16[c,d]	CuI	none	Ag_2CO_3	toluene	(71)

[a] Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2a** (2.0 equiv), solvent (2.5 mL), 10 h. [b] GC yield; the yield of the isolated product is in parentheses. [c] 3.0 equiv of **2a** and 4.0 equiv of *t*BuOLi were used. [d] 10 mol % of CuI was used.

Scheme 1. Cu-Catalyzed Dehydrogenative Cross-Coupling of Benzothiazoles **1** with Thiazoles **2**[a]

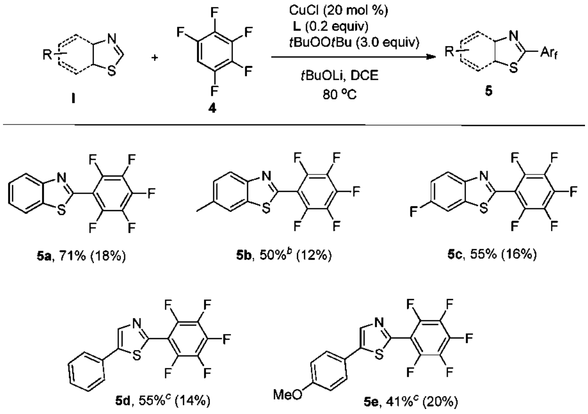


[a] Reaction conditions (unless otherwise specified): **1** (0.3 mmol, 1.0 equiv), **2** (2.0−3.0 equiv), *t*BuOLi (3.0−4.0 equiv), toluene (2.5 mL), 10 h, 80 °C. All reported reaction yields are isolated yields. The number in parentheses is the homocoupling yield of compound **1**.

5-Arylthiazoles are also suitable substrates, providing **3k**−**n** in good yields (**3k**−**n**). However, oxazoles and benzimidazoles are not suitable substrates under standard reaction conditions.

Encouraged by these results, we proceeded to employ this copper-catalyzed direct diaryl cross-coupling protocol to the synthesis of 2-polyfluoroarylthiazoles. Because not only this kind of fluorinated compounds can be used as a fluorescent probe,[13] but also polyfluoroarylated compounds play an important role in life and materials science.[14] In addition, to the best of our knowledge, methods for construction of this structural motif through transition-metal catalyzed dehydrogenative cross-coupling have not been reported so far.[15] However, under the same reaction conditions, no desired product **5a** was observed, when benzothiazole **1a** and pentafluoroarene **4** were tested. After a survey of reaction parameters (for details see Supporting Information), the reaction efficiency was significantly improved by using CuCl (0.2 equiv) as the catalyst, 4,4′-dimethoxy-2,2′-bipyridine **L** (0.2 equiv) as the ligand, *t*BuOO*t*Bu as the oxidant, and 1,2-dichloroethane (DCE) as the solvent (Scheme 2). Different thiazoles were then investigated. Generally, the electronic effect plays an important role in the reaction efficiency. As shown in Table 3,

Scheme 2. Cu-Catalyzed Dehydrogenative Cross-Coupling of Benzothiazoles **1** with Pentafluorobenzene **4**[a]



[a] Reaction conditions (unless otherwise specified): **1** (2.0 equiv), **4** (0.3 mmol, 1.0 equiv), *t*BuOLi (0.5 equiv), DCE (2.5 mL), 6 h, 80 °C. All reported reaction yields are isolated yields. The number in parentheses is the homocoupling yield of compound **4**. **L**, 4,4′-dimethoxy-2,2′-bipyridine. [b] 2.5 equiv of *t*BuOLi were used. [c] 1.5 equiv of *t*BuOLi were used.

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benzothiazole **1a** furnished the corresponding product **5a** in good yield, but both electron-rich and -deficient benzothiazoles led to slightly lower yields (**5b**–**c**). 5-Arylthiazoles are also suitable substrates with reasonable yields obtained (**5d**–**e**).

While a detailed reaction mechanism of this transformation remains to be elucidated, on the basis of previous research on the copper-catalyzed homocoupling of arenes or heteroarenes,[5] we proposed that the present direct diaryl cross-coupling may begin with the base promoted cupration of one of the coupling partner (heteroarene or polyfluoroarene), which then reacts with the other partner copper species (heteroaryl or polyfluoroarylcoper species) or lithium species (heteroaryl or polyfluoroaryl lithium) generated by the reaction of heteroarene or polyfluoroarene with *t*BuOLi to form key intermediate biheteroaryl or heteroarylpolyfluoroaryl copper complex **I**. **I** undergoes reductive elimination in the presence of oxidant, silver salt or *t*BuOO*t*Bu,[16] to deliver the desired product and release the copper to complete the catalytic cycle.

In conclusion, a copper-catalyzed dehydrogenative cross-coupling of benzothiazoles with thiazoles and polyfluoroarene has been demonstrated. High levels of selectivity for the cross-coupled products over homocoupling of either coupling partner were generally observed. The notable features of this reaction are its mild reaction conditions, synthetic simplicity, and usage of less expensive copper as the catalyst. We believe that these intriguing results should prompt a much wider examination of this copper-catalyzed direct diaryl cross-coupling chemistry. Further studies to expand the substrate scope and uncover the reaction mechanism are now in progress.

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

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(16) A Cu(III) complex is supposed to be formed in the presence of oxidant before reductive elimination. However, the detailed mechanism at this stage unclear and will be addressed in the future.

The authors declare no competing financial interest.