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Copper(II)-Mediated Dehydrogenative Cross-Coupling of Heteroarenes

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ABSTRACT

$Cu(OAc)_2$-mediated dehydrogenative cross-coupling between two heteroarenes has been realized in the absence of any other additive. A mechanism involving a formal Cu(II) to Cu(0) route by convergent disproportionation of the copper mediator is proposed and has been evidenced by copper mirror formation during the reaction. This synthetic protocol provides a concise and "green" access to unsymmetrical biheteroarenes bearing structural motifs of substantial utility in organic synthesis.

Bi(heteroaryl) structural motifs usually possess interesting biological and physical properties and have been extensively applied in the preparation of pharmaceuticals and advanced materials.[1] The traditional synthetic route to biheteroarenes (heteroaromatic biaryls) is transition-metal-catalyzed cross-coupling of a heteroaryl halide with another preactivated heteroaryl substrate.[2] During the past decades, much effort was made toward the direct arylation/heteroarylation of heteroaromatic C−H bonds.[3,4] In this context, direct C−H/C−H cross-coupling between two heteroarenes represents the most concise route to biheteroarenes.[5,6] A palladium catalyst combined with a stoichiometric amount of metal oxidants such as Cu(II), Cu(II)/Ag(I), or Cu(II)/Cu(I) reagents was usually required (Scheme 1, path A).[7] A stepwise procedure was developed by Daugulis et al. for the synthesis of unsymmetrical biheteroarenes via a base-mediated deprotonation/iodination and Cu(I)-catalyzed C−H arylation sequence (path B).[8] From the viewpoint of economical and environmental consideration, it is highly desirable to employ less expensive metal catalysts/mediators and avoid the

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use of halogens, and thus, copper is considered as a good metal candidate because of its relatively low cost and toxicity.

During our ongoing investigation on copper-mediated direct C−H functionalization of heteroarenes,[9] we envisioned that a proper copper salt might promote the C−H/C−H cross-coupling between two different heteroarenes. Herein, we report a copper(II)-mediated intermolecular dehydrogenative cross-coupling between five-membered heteroarenes (Scheme 1, path C). Such a cross-coupling reaction was accomplished in the absence of any other additive by means of a Cu(II) mediator under Pd- and halogen-free conditions. Preliminary mechanistic studies reveal that convergent disproportionation of Cu(II) and Cu(I) was involved in the reaction (Scheme 1).[10,11]

Scheme 1. Dehydrogenative Cross-Coupling of Heteroarenes

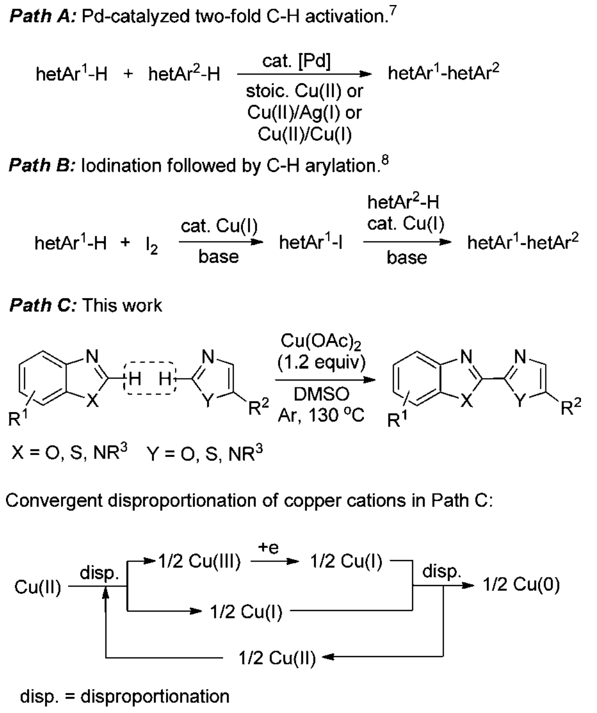
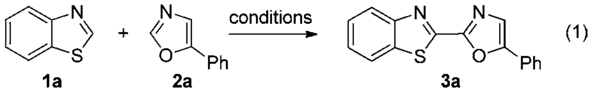


Table 1. Screening Conditions for the Reaction of **1a** and **2a**[a]



entry	mediator	additive[b]	solvent	yield (%)[c]
1	$Cu(OAc)_2\cdot H_2O$		DMSO	62
2[d]	$Cu(II)X_n$		DMSO	nd
3	$Cu(OAc)_2$		DMSO	81
4[e]	CuX		DMSO	nd
5	CuOAc		DMSO	23
6	$Cu(OAc)_2$	Na_2CO_2	DMSO	23
7	$Cu(OAc)_2$	AcOH	DMSO	50
8	$Cu(OAc)_2$	PivOH	DMSO	46
9[f]	$Cu(OAc)_2$		DMSO	42
10[f]	$Cu(OAc)_2$	BQ	DMSO	28
11[f]	$Cu(OAc)_2$	$K_2S_2O_8$	DMSO	<1
12[f]	$Cu(OAc)_2$	DDQ	DMSO	<1
13[g]	$Cu(OAc)_2$	O_2	DMSO	7
14	$Cu(OAc)_2$		DMF	65
15	$Cu(OAc)_2$		dioxane	23
16	$Cu(OAc)_2$		*O*-xylene	73
17[h]	$Cu(OAc)_2$		DMSO	70
18[i]	$Cu(OAc)_2$		DMSO	52
19[j]	$Cu(OAc)_2$		DMSO	91 (84)
20[k]	$M(OAc)_2\cdot 4H_2O$		DMSO	nd

[a] Conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), mediator (0.3 mmol), solvent (3 mL), 0.1 MP Ar, 130 °C, 12 h. [b] 2 equiv. [c] GC yields with isolated yield in parentheses. [d] X = F, Cl, Br, SO_4, NO_3, CO_3, OTf, or O_2CCF_3; *n* = 1 or 2. [e] X = Cl or I. [f] 0.5 equiv of $Cu(OAc)_2$. [g] 0.1 MPa. [h] 150 °C. [i] 110 °C. [j] 1.2 equiv of $Cu(OAc)_2$. [k] M = Fe, Mn, Ni, or Co.

Initially, the 1:1 molar ratio reaction of benzothiazole (**1a**) and 5-phenyloxazole (**2a**) was carried out in the presence of $Cu(OAc)_2\cdot H_2O$ (1 equiv) in DMSO at 130 °C under an argon atmosphere, forming the desired product **3a** in 62% yield within 12 h (Table 1, entry 1). Other divalent copper(II) salts such as CuF_2, $CuCl_2$, $CuBr_2$, $CuSO_4$, $Cu(NO_3)_2$, $CuCO_3$, $Cu(OTf)_2$, and $Cu(O_2CCF_3)_2$ were completely ineffective in the reaction (entry 2), revealing that OAc anion was crucial to the reaction. However, AcOH itself did not show any catalytic activity. With anhydrous $Cu(OAc)_2$ as the mediator, the yield was increased to 81% (entry 3). Cu(I) salts, CuI and CuCl, failed to effect the reaction (entry 4). Use of CuOAc (1 equiv) provided 23% yield (entry 5), which might be caused by the partial disproportionation of copper(I) to copper(0) and copper(II), and the latter then served as the real catalyst/mediator for the reaction.[12] Base and acid additives did not improve the yield (entries 6−8). Lowering the amount of $Cu(OAc)_2$ to 0.5 equiv led to a lower yield (42%, entry 9). Attempts to improve the reaction efficiency by using a catalytic amount of $Cu(OAc)_2$ (0.5 equiv) and oxidants such as 1,4-benzoquinone (BQ), $K_2S_2O_8$ and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) failed (entries 10−12). Surprisingly, the reaction proceeded very slowly under an oxygen atmosphere (entry 13). Solvents DMF, dioxane, and *o*-xylene were inferior to DMSO (entries 14−16). Raising or lowering the temperature deteriorated the reaction (entries 17 and 18). Use of an excess amount of $Cu(OAc)_2$ (1.2 equiv) improved the yield to 91% (entry 19).[13] It should be noted that the reaction did not occur in

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(9) (a) Yang, F.; Xu, Z.; Wang, Z.; Yu, Z. K.; Wang, R. *Chem.—Eur. J.* **2011**, *17*, 6321. (b) Dai, C.; Xu, Z.; Huang, F.; Yu, Z. K.; Wang, R. *J. Org. Chem.* **2012**, *77*, 4414.

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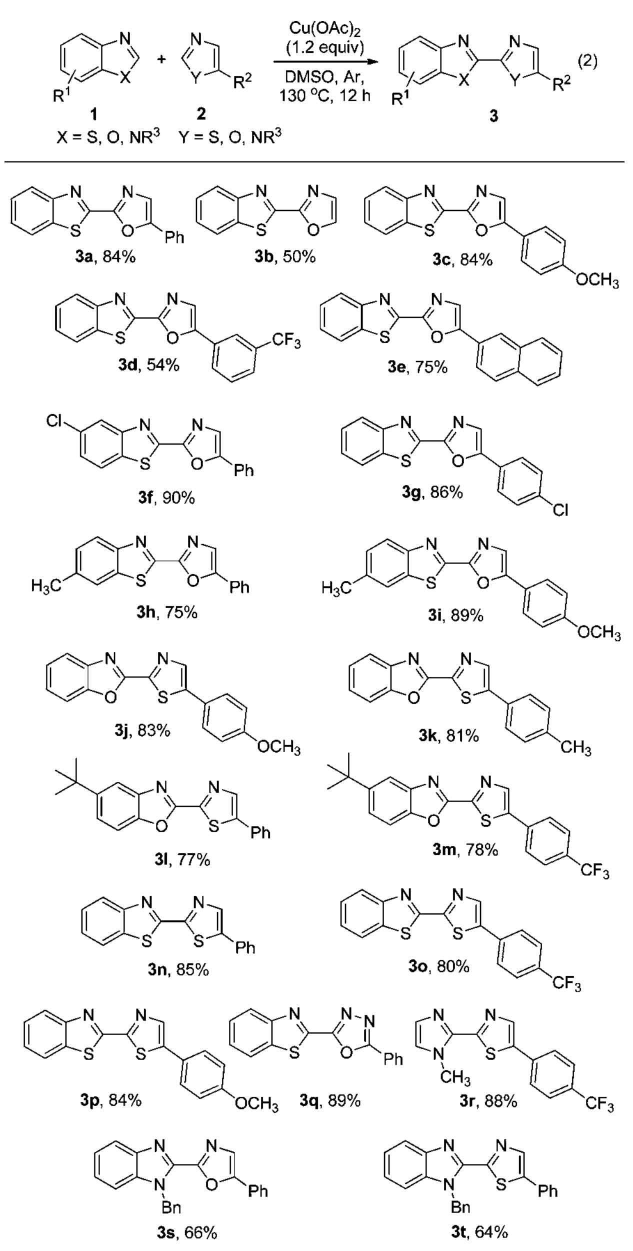
(12) Increasing the amount of CuOAc to 3 equiv improved the yield to 43%.

Scheme 2. Cu(II)-Mediated Dehydrogenative Cross-Coupling of Heteroarenes[a]



[a] Conditions; **1** (0.5 mmol), **2** (0.5 mmol), Cu(OAc$_2$) (0.6 mmol), 5 mL of DMSO, 0.1 MPa Ar. [b] Isolated yields.

the absence of Cu(OAc)$_2$. Finally, with other transition-metal acetates such as Fe(OAc)$_2$·4H$_2$O, Mn(OAc)$_2$·4H$_2$O, Ni(OAc)$_2$·4H$_2$O, and Co(OAc)$_2$·4H$_2$O, no desired product was obtained (entry 20).

Under the optimized conditions as shown for entry 19 in Table 1, the protocol generality was explored (Scheme 2). Benzothiazoles smoothly reacted with azoles regardless of the electronic and steric properties of the substituents, providing biheteroarenes **3a**−**i** in good yields (50−90%). It is noteworthy that the reactions of 5-chlorobenzothiazole with 5-phenyloxazole and benzothiazole with 5-(4-chlorophenyl)oxazole efficiently proceeded to form **3f** (90%) and **3g** (86%), respectively, with the chloro substituents untouched during the reaction, which render the biheteroarene products good opportunities for further transformations such as transition-metal-catalyzed functionalization of the C−Cl bond. The reactions of benzoxazoles with thiazoles proceeded well with good tolerance of electron-donating and -withdrawing substituents (**3j**−**m**). Highly selective C−H/C−H cross-coupling between two analogous heteroarenes, e.g., benzothiazole and 5-arylthiazoles, was also achieved under the same conditions (**3n**−**p**). Oxadiazole was a compatible substrate, and it was efficiently coupled with benzothiazole to afford **3q** in 89% yield. Imidazole and benzimidazole have been proven to be more sluggish in reactivity than thiazoles and azoles, which often require relatively harsh conditions for their C−H bond cleavage at the C2 position(s).[14] We were pleased to find that under the stated conditions, *N*-methylimidazole and *N*-benzylbenzimidazole smoothly reacted with 5-phenylthiazole and 5-phenyloxazole, furnishing the corresponding biheteroarenes in moderate to good yields (**3r**−**t**), respectively. It should be noted that in all the reactions as shown in Scheme 2, a shining red-brown copper mirror and some Cu(0) powder were observed on the glass wall and bottom of the reaction vessel (Figure 1), revealing Cu(0) formation during the reaction.

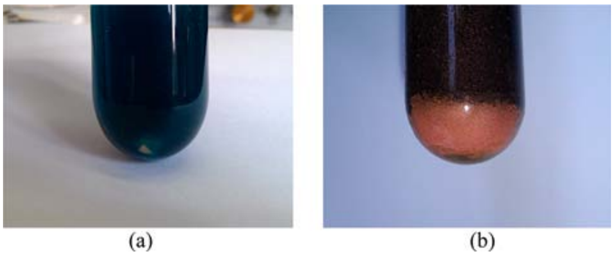


Figure 1. Copper mirror formation: (a) prior to heating; (b) after the reaction was complete.

To gain insight into the reaction mechanism, a kinetic isotope effect (KIE) competition experiment was carried out by using the reaction of **1a** with **2a** and that of their corresponding derivatives deuterated at C2 positions ([D]-**1a** and [D]-**2a**) (Supporting Information). No kinetic isotope effect (k_H/k_D = 1.07) was observed, suggesting that C−H bond cleavage at the C2 position(s) of the heteroarene substrates was not involved in the rate-determining step in the overall catalytic cycle.[15] Recently, Yu[16a] and

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(13) About 3% of homocoupling product from **1a** was observed in the reaction. The byproduct was readily separated by silica gel column chromatography.

(14) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

(15) For Cu-mediated azole C−H arylations in which C−H bond cleavage was not involved in the rate-determining step, see refs 4d and 19.

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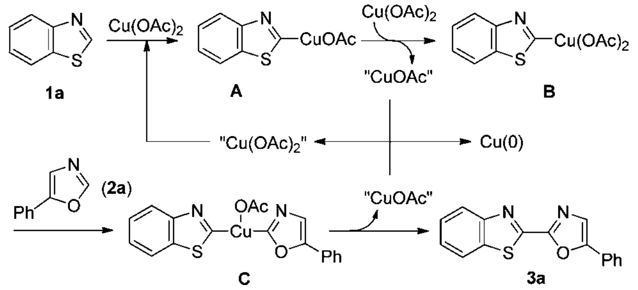
Kündig[16b] reported the copper(II)-mediated arene C–H/C–H cross-coupling through a radical pathway, respectively. However, when the reaction of **1a** and **2a** was carried out in the presence of an equimolar amount of Cu(OAc)$_2$ and TEMPO, a radical scavenger,[17] **3a** was almost collected in the same yield (87%), suggesting that a radical mechanism can be excluded for this transformation (Supporting Information). Acetate anion-facilitated formation of the desired product (Table 1, entries 1–3) supports a mechanism involving the carboxylate-ligand-assisted concerted metalation–deprotonation (CMD) process of a heteroarene C–H bond.[18,19]

Theoretically, there are two possibilities for a copper cation to undergo disproportionation: (i) Cu(II) to Cu(III) and Cu(I); (ii) Cu(I) to Cu(II) and Cu(0). In our case, the initially in situ generated organocopper(II) species by a CMD process may be disproportionated to Cu(III) and Cu(I).[10] The Cu(III) species facilitates the second CMD process and then is reductively eliminated to release a Cu(I) species.[10,19] Recently, Miura and co-workers disclosed a copper(II)-mediated dehydrogenative cross-coupling between azoles and 2-arylpyridines via a possible disproportionation of Cu(II) to Cu(III) and Cu(I) pathway by means of more than 2 equiv of Cu(II) salt.[19] However, in our case, 1 equiv of Cu(OAc)$_2$ could promote the reaction to a good conversion (Table 1, entry 3), which suggests that a subsequent disproportionation of the resultant Cu(I) species to Cu(0) and Cu(II) might happen, and the latter would promote the next catalytic cycle. The copper mirror observed in the reaction revealed the formation of Cu(0). The Cu(0) species cannot be reoxidized to Cu(I) or Cu(II) under the stated conditions. It was observed that the added CuOAc did not promote the reaction very efficiently (Table 1, entry 5),[12] presumably due to its less efficient disproportionation to form Cu(II) than the in situ generated Cu(I) species.

On the basis of the experimental results and the above consideration, the plausible mechanism involving a convergent disproportionation of Cu(II) and Cu(I) cations is proposed for the dehydrogenative cross-coupling of **1a** and **2a** in Scheme 3. The reaction sequence is initiated by a CMD process of the relatively more acidic heteroarene[20] **1a**'s C–H bond, forming intermediate **A**.[18,19] Its subsequent disproportionation aided by another molecule of Cu(OAc)$_2$ forms Cu(III) intermediate **B** and Cu(I). The second CMD process of **2a**'s C–H bond promoted by **B** results in biheteroarylcopper(III) species **C**. Reductive elimination of **C** affords the desired cross-coupling product **3a** along with Cu(I), which then is disproportionated to Cu(0) and Cu(II) for the next reaction cycle, featuring a convergent disproportionation pathway for the copper(II) mediator.[11] The competitive deuterium-labeling experiment suggests that the reductive elimination or disproportionation step might be the rate-determining step. However, at the present stage, the pathway via nucleophilic addition to heteroarene C═N by a heteroarene-metal intermediate such as intermediate **A** followed by an oxidative rearomatization to give heterobiaryl cannot be ruled out.[21]

Scheme 3. Proposed Mechanism



In conclusion, we have developed an efficient copper(II)-mediated process for the direct synthesis of heteroaromatic biaryls via dehydrogenative cross-coupling of heteroarenes through convergent disproportionation of the mediator. This synthetic protocol provides a concise access to unsymmetrical biheteroarenes bearing structural motifs of substantial utility in organic synthesis.

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

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[17] For an example of TEMPO used as a radical trap, see: Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506.

[18] A review on carboxylate-ligand-assisted CMD, see: Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

[19] The carboxylate-ligand-assisted CMD process was proposed in Cu(OAc)$_2$-mediated azole C–H bond cleavage; see: Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160.

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[21] For transition-metal-catalyzed azole (thiazole) C–H functionalizations via electrophilic addition/oxidative rearomatization sequence, see: (a) Wertz, S.; Kodama, S.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11511. (b) Ranjit, S.; Lee, R.; Heryadi, D.; Shen, C.; Wu, J.; Zhang, P. F.; Huang, K.-W.; Liu, X. G. *J. Org. Chem.* **2011**, *76*, 8999.

The authors declare no competing financial interest.