Synthetic Methods

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Copper-Mediated and Copper-Catalyzed Cross-Coupling of Indoles and 1,3-Azoles: Double C–H Activation**

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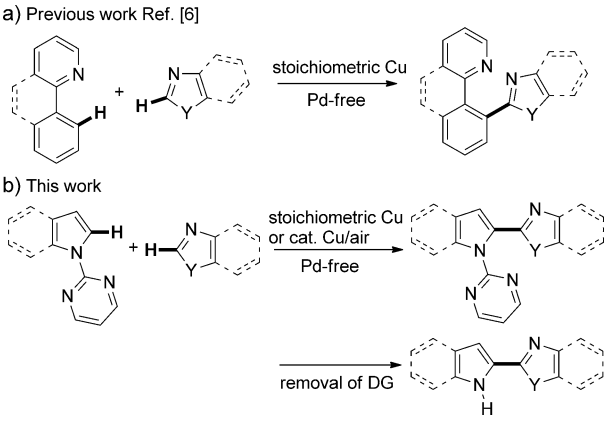
Since biaryl structures that contain an indole nucleus occur in many pharmaceuticals, biologically active compounds, and functional materials, indole–arene cross-coupling reactions have received great attention from synthetic chemists.[1] In particular, recent developments in metal-mediated direct C–H functionalization[2] enable a direct cross-coupling of unactivated indoles and arenes as an ideal and attractive alternative to the conventional cross-coupling technology with organic halides or organometallic reagents.[3] However, reported protocols generally depend on precious palladium catalysts combined with copper- or silver-based terminal oxidants. Thus, further developments for new reactions mediated by other transition metals are strongly desired, since they can provide a complementary and unique selectivity as well as higher efficiency and versatility toward the dehydrogenative synthesis of indole–arene conjugates. Meanwhile, significant attention has been recently focused on copper salts and catalysts as an inexpensive and potentially more effective alternative to the above palladium catalysts, and copper-promoted C–H arylations of some (hetero)arenes with aryl (pseudo)halides[4] and aryl metals[5] now become possible. Moreover, our group also succeeded in the cross-coupling with unfunctionalized arenes (Scheme 1 a).[6] Herein, we introduce a copper salt as a new promising promoter in the direct coupling between indoles and 1,3-azoles. The key to our success is the installation of a suitable 2-pyrimidyl director on the indole nitrogen atom; this group is readily removable after the coupling event. Moreover, the use of atmospheric oxygen is found to render the reaction catalytic in copper (Scheme 1 b).



Scheme 1. Cu-promoted intermolecular direct biaryl coupling. DG = directing group.

Our study commenced by an identification of an appropriate substituent on the indole nitrogen atom under Cu(OAc)$_2$·OH$_2$/PivOH-mediated conditions based on the previous work[6] (Table 1). While indoles that bear Me, Ph, and (2-pyridyl)sulfonyl[7] groups completely failed to couple with benzoxazole (**2a**; Table 1, entries 1–3), an *N*-(2-pyridyl)indole (**1a-2Py**)[8] was a promising candidate (entry 4). The result of a control experiment with *N*-(4-pyridyl)indole (**1a-4Py**) indicates a pivotal role of the directing effect of nitrogen to the copper center (Table 1, entry 5). Pleasingly, a more easily attachable and detachable 2-pyrimidyl group[8b,c] showed a comparable efficiency as the *N*-(2-pyridyl)indole **1a-2Py** (Table 1, entries 6 and 4). With the *N*-(2-pyrimidyl)indole **1a** as the optimized indole substrate, other reaction parameters were screened next. Anhydrous Cu(OAc)$_2$ slightly improved the yield (Table 1, entry 7), whereas the use of $CuCl_2$ or Cu(OTf)$_2$ instead of Cu(OAc)$_2$·OH$_2$ completely shut down the reaction (Table 1, entries 8 and 9). Investigation of the reaction stoichiometry and the use of some additives revealed that the desired heteroarylated indole **3aa** was isolated in 94% yield when anhydrous Cu(OAc)$_2$ and AcOH were employed (Table 1, entry 11). Even in the absence of AcOH, the reaction proceeded, but the yield was somewhat lower (Table 1, entry 12). Notably the Cu-based cross-coupling occurred exclusively at the indole C2-position; this selectivity is complementary to the precedent Pd-based methodology.[3f]

By using the conditions indicated in entry 11 of Table 1, we evaluated the scope of the direct indole/1,3-azole coupling. Representative products are illustrated in Scheme 2. In addition to the simple benzoxazole **2a**, some 5-substituted benzoxazoles could couple with **1a** (**3ab–ad**). Various monocyclic 5-aryloxazoles also could be employed to form the corresponding biheteroaryls **4aa–af** at synthetically useful levels. Notably, electron-donating methyl and methoxy as well as electron-withdrawing chloro, nitro, and cyano groups were tolerated during the reaction. On the other hand, benzothiazole and *N*-methylbenzimidazole in place of the oxazoles could be reacted, albeit with lower efficiency (**5** and **6**). Other

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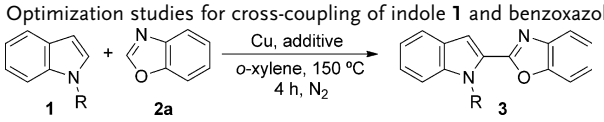
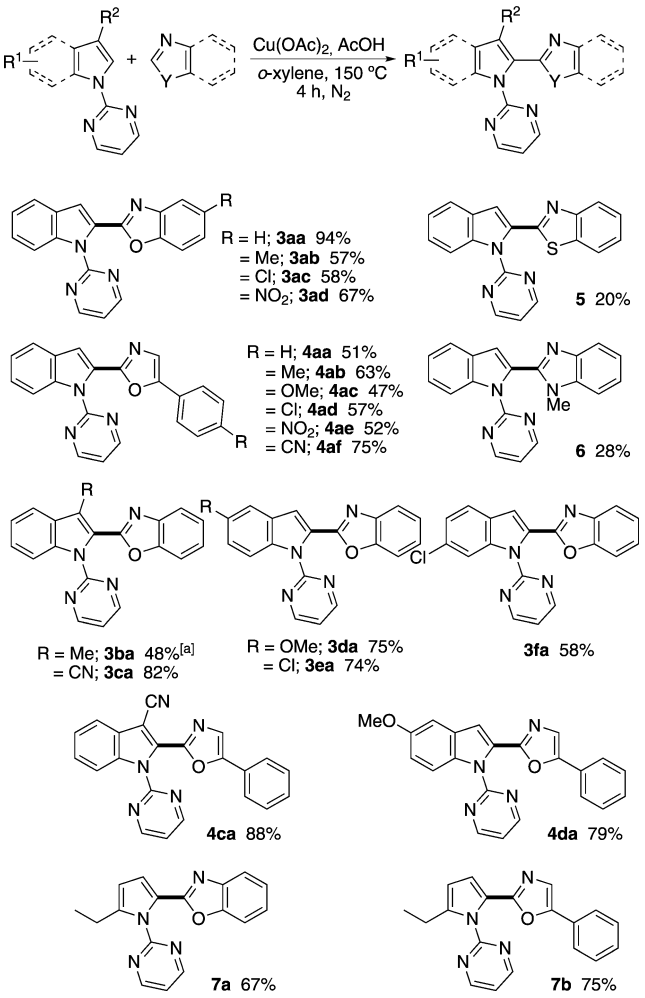
Table 1: Optimization studies for cross-coupling of indole **1** and benzoxazole **2a**.[a]



Entry	R (**1**)	Cu salt/additive	**3**, Yield [%][b]
1	Me (**1a-Me**)	$Cu(OAc)_2{\cdot}OH_2$/PivOH	**3aa-Me**, 0
2	Ph (**1a-Ph**)	$Cu(OAc)_2{\cdot}OH_2$/PivOH	**3aa-Ph**, 0
3	SO_2(2-pyridyl) (**1a-SO_2Py**)	$Cu(OAc)_2{\cdot}OH_2$/PivOH	**3aa-SO_2Py**, 0
4	2-pyridyl (**1a-2Py**)	$Cu(OAc)_2{\cdot}OH_2$/PivOH	**3aa-2Py**, 56
5	4-pyridyl (**1a-4Py**)	$Cu(OAc)_2{\cdot}OH_2$/PivOH	**3aa-4Py**, 0
6	2-pyrimidyl (**1a**)	$Cu(OAc)_2{\cdot}OH_2$/PivOH	**3aa**, 55
7	2-pyrimidyl (**1a**)	$Cu(OAc)_2$/PivOH	**3aa**, 69
8	2-pyrimidyl (**1a**)	$CuCl_2$/PivOH	**3aa**, 0
9	2-pyrimidyl (**1a**)	$Cu(OTf)_2$/PivOH	**3aa**, 0
10[c]	2-pyrimidyl (**1a**)	$Cu(OAc)_2$/PivOH	**3aa**, 82
11[c]	2-pyrimidyl (**1a**)	$Cu(OAc)_2$/AcOH	**3aa**, (94)
12	2-pyrimidyl (**1a**)	$Cu(OAc)_2$/none	**3aa**, 83

[a] Reaction conditions: Cu salt (0.50 mmol), additive (0.25 mmol), indole (0.25 mmol), **2a** (0.50 mmol), *o*-xylene (1.5 mL), 150 °C, N_2. [b] Yield estimated by GC method. Yield of isolated product given in parenthesis. [c] With $Cu(OAc)_2$ (0.75 mmol). OTf = trifluoromethanesulfonate, Piv = *tert*-butylcarbonyl.



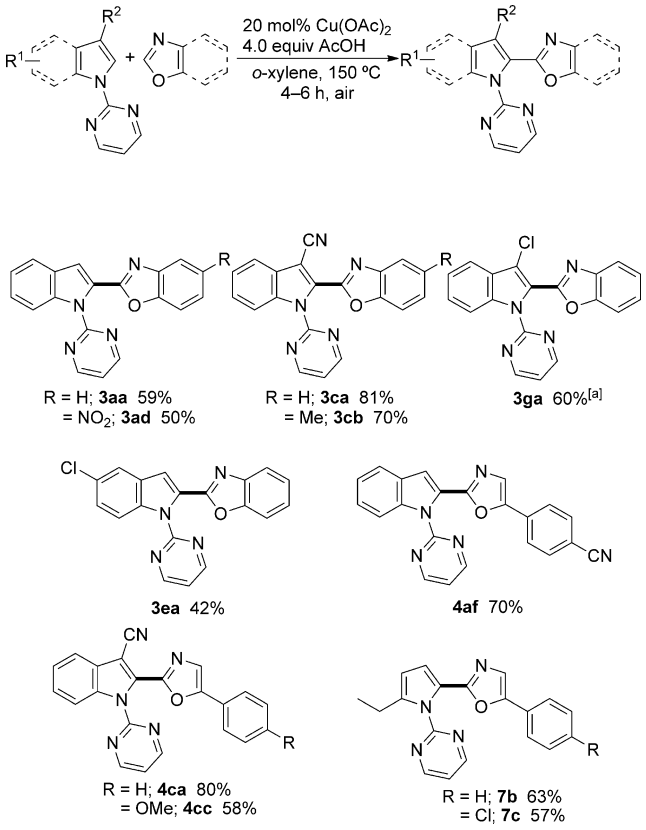
Scheme 2. Products of copper-mediated cross-coupling of *N*-(2-pyrimidyl)indoles or -pyrroles and 1,3-azoles. The reaction was performed by using the conditions in Table 1, entry 11. The yields are of the isolated products. [a] At 170 °C for six hours.

electron-deficient arenes, such as pentafluorobenzene and pyridine *N*-oxide, resulted in no formation of the corresponding biaryls (data not shown). The generality of the indole substrate was subsequently investigated. While 3-methylindole resulted in a moderate yield of **3ba** even at higher temperature, its cyano analogue underwent the coupling very smoothly to afford **3ca** in a good yield. The Cu-based reaction tolerated the methoxy and chloro substituents on the benzene ring (**3da**–**fa**). Moreover, a pyrrole nucleus was also available for use: the cross-coupling with benzoxazole and 5-phenyloxazole took place without any difficulty to make the pyrrole–oxazole linkage directly in 67 and 75% yields, respectively (**7a** and **7b**).

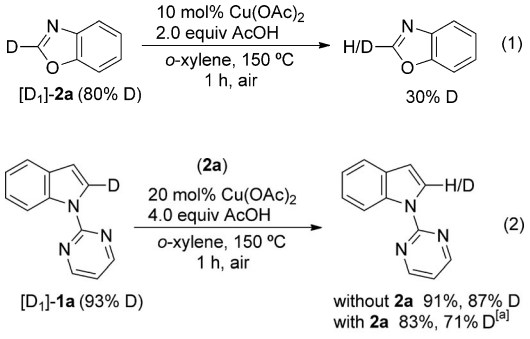
Although the above protocol, which uses stoichiometric amounts of Cu, deserves significant attention owing to some benefits associated with inexpensiveness and relatively low toxicity of copper salts, the development of catalytic variants is quite appealing from the economical and synthetic points of view. After an extensive survey of terminal co-oxidants, we were pleased to find that the most attractive and ideal co-oxidant atmospheric oxygen could make the reaction catalytic in copper. Our preliminary but intriguing results are shown in Scheme 3. In a typical experiment, treatment of *N*-(2-pyrimidyl)indole **1a** (0.25 mmol) with benzoxazole **2a** in the presence of $Cu(OAc)_2$ (20 mol%) and AcOH (4.0 equiv) in boiling *o*-xylene under atmospheric conditions produced **3aa** in 59% yield. The copper catalysis could be applied to various combinations of substituted indoles and benzoxazoles (**3**). Particularly notable is the satisfying formation of the 2-chloroindole derivative **3ga**, which is otherwise difficult to obtain under the stoichiometric conditions in Scheme 2, because of the competitive dechlorination. Moreover, some 5-aryloxazoles could be employed with good efficiencies (**4**). The conjugated pyrrole–oxazole cores were also readily accessible even under catalytic conditions (**7**). In some cases, homocoupling products of oxazoles were observed (ca. 2–8% based on 1,3-azoles; GC). The competitive reaction can inform us about the reaction mechanism (see below). To our knowledge, this is the first example of the copper-catalyzed intermolecular direct biaryl cross-coupling.[9]

To get some insights into the reaction mechanism, some deuterium-labeling experiments were conducted. The exposure of 2-deuteriobenzoxazole [D_1]-**2a** alone to the catalytic conditions induced the rapid H/D scrambling after one hour [Eq. (1)]. In the absence of $Cu(OAc)_2$, no H/D scrambling of [D_1]-**2a** was observed. In contrast, the exposure of 2-deuterioindole [D_1]-**1a** to catalytic conditions resulted in only a minor drop of the deuterium content, while the addition of benzoxazole **2a** accelerated the H/D exchange reaction of [D_1]-**1a** [Eq. (2); the values 91% and 83% are the amounts of isolated recovered material].

Based on these outcomes, we propose the reaction mechanism for the catalytic coupling of **1a** with **2a** as follows (Scheme 4). An initial carboxylate-ligand-assisted cupration of the relatively acidic C–H bond of **2a**[10] generates hetero-

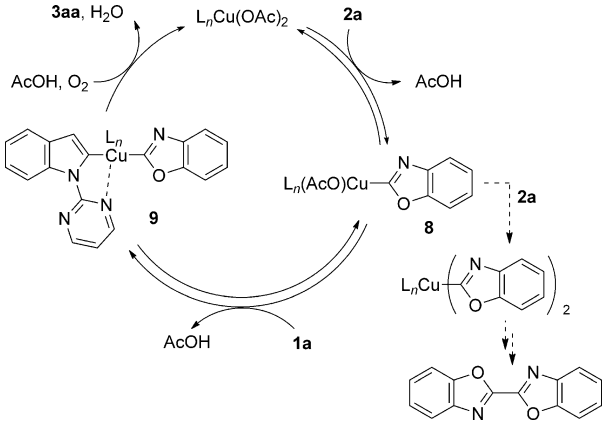


Scheme 3. Copper-catalyzed cross-coupling of *N*-(2-pyrimidyl)indoles or -pyrrole and 1,3-azoles. Reaction conditions: $Cu(OAc)_2$ (0.050 mmol), AcOH (1.0 mmol), indole (0.25 mmol), 1,3-azole (0.50 mmol), *o*-xylene (1.5 mL), 150 °C, air. The yields are of the isolated products. [a] Contaminated with a trace amount of the product from dechlorination.



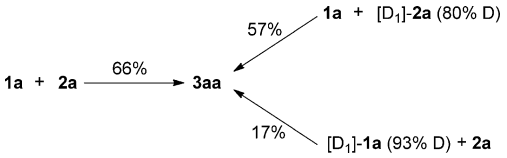
[a] ca. 10% of **3aa** was also detected.

arylcopper intermediate **8**.[11] The formation of homocoupling byproducts of 1,3-azoles that were observed during the reaction shown in Scheme 3 can be consistent with the proposed intermediate.[12] The competitive cupration of the second benzoxazole generates a bis(benzoxazole)copper, en route to the homocoupling product. Subsequent chelation-assisted C–H metalation of **1a** occurs to form the bis(heteroaryl)copper species **9** as a key intermediate. The phenomenon seen in Eqs. (1) and (2) is highly suggestive of reversible C–H bond cleavage of each substrate. Final O_2-promoted



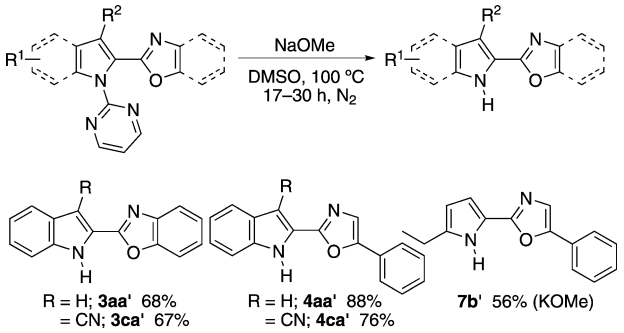
Scheme 4. Plausible reaction mechanism. L = AcOH, O_2, or solvent.

irreversible reductive elimination[13] provides the product **3aa** along with regeneration of the starting copper complex to complete the catalytic cycle. The postulated metalation order (1,3-azole then indole) can account for the observation that the loss of deuterium of [D_1]-**1a** was accelerated by addition of **2a** in Eq. (2). The highly electron-withdrawing nature of the benzoxazole ligand in **8** might facilitate a coordination of the pyrimidyl nitrogen atom to the copper center to trigger the second C–H metalation. At this stage, we speculate that this highly electron-deficient nature of the 1,3-azolyl ligand on **8** is key to the preference for cross-coupling over homocoupling. Although the minor but significant H/D exchange at the indole C2-position interfered with calculation of a correct kinetic isotope effect (KIE) value, comparison of production rates of **3aa** in a set of the following three experiments informs us about the rate-determining step of the reaction (Scheme 5): the introduction of deuterium into benzoxazole **2a** had little influence on the yield of **3aa**, whereas the use of



Scheme 5. Comparison of production rates of **3aa** with deuterium-labeled **1a** or **2a**. Conditions: $Cu(OAc)_2$ (0.75 mmol), AcOH (0.25 mmol), **1a** or [D_1]-**1a** (0.25 mmol), **2a** or [D_1]-**2a** (0.50 mmol), *o*-xylene (1.5 mL), 150 °C, N_2, one hour.

[D_1]-**1a** instead of unlabeled **1a** induced a large drop in the yield even under otherwise identical conditions. Thus, the C–H bond cleavage of **1a** would be the most plausible rate-limiting step.[14] However, at the present, we cannot completely exclude an alternative pathway that includes 1) formation of an indolylcopper species through a chelation-assisted C–H cupration of indoles, 2) insertion of the C=N double bond of 1,3-azoles to the C–Cu bond, and 3) oxidation leading to rearomatization of azole cores.[15] Additional efforts are essential for clarification of the detailed mechanism; studies are ongoing in our laboratory.[16]



Scheme 6. Removal of 2-pyrimidyl director.

Finally, we attempted to remove the directing group from the coupling products (Scheme 6). Upon treatment of benzoxazole-substituted **3aa** and **3ca** with NaOMe in dimethylsulfoxide (DMSO) at 100 °C,[8b] the corresponding N-H indoles **3aa′** and **3ca′** were obtained in 68 and 67 % yields, respectively. The free N-H indole/oxazole/benzene-conjugated aromatic cores **4aa′** and **4ca′** were also available by using the same procedure. For the removal of the 2-pyrimidyl director from the pyrrole ring, the use of KOMe instead of NaOMe was found to be more effective (**7b′**).

In conclusion, we have developed a copper-mediated intermolecular cross-coupling of indoles and 1,3-azoles with the chelation assistance of a 2-pyrimidyl group. Moreover, a catalytic variant also has been achieved by using atmospheric oxygen as the sole oxidant. The process can be regarded as one of the most environmentally benign, ideal cross-couplings with the liberation of H_2O as the sole byproduct. The Cu/O_2 catalysis can provide a new opportunity to a direct, catalytic dehydrogenative biaryl coupling through dual C–H bond cleavage and additionally contribute to the synthetic utility of copper complexes in the field of C–H functionalization. Further studies seek to uncover the detailed reaction mechanism, improve the turnover number, and expand the scope of arene coupling partners.

Experimental Section

Copper-catalyzed cross-coupling of 1-(pyrimidin-2-yl)-1*H*-indole (**1a**) and benzoxazole (**2a**; Scheme 2) to give **3aa**: $Cu(OAc)_2$ (9.0 mg, 0.050 mmol), acetic acid (60 mg, 1.0 mmol), 1-(pyrimidin-2-yl)-1*H*-indole (**1a**, 49 mg, 0.25 mmol), benzoxazole (**2a**, 60 mg, 0.50 mmol), *o*-xylene (1.5 mL), and 1-methylnaphthalene (ca. 20 mg, internal standard) were placed in a 20 mL two-necked reaction flask equipped with a reflux condenser and a drying tube lined with calcium chloride. The solution was stirred at 150 °C for four hours in air. The consumption of **1a** was confirmed by GC analysis, and the resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate. Concentration in vacuo followed by silica gel column chromatography with hexane/ethyl acetate (2:1, v/v) gave 2-{1-(pyrimidin-2-yl)-1*H*-indol-2-yl}benzoxazole (**3aa**, 46 mg, 0.15 mmol) in 59 % yield.

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[13] Although the exact role of O_2 is not clear at this stage, an O_2-promoted oxidation process of Cu^{II} into Cu^{III} might be involved prior to the reductive elimination. In the case of the stoichiometric reaction under N_2, a disproportionation of Cu^{II} into Cu^{I} and Cu^{III} can be alternative; a) L. M. Huffman, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 9196; b) A. E. King, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 5044; c) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068.
[14] The exact mechanism of C–H bond cleavage of **1a** still remained obscure, but the major impact of deuterium incorporation on the production rate of **3aa** (Scheme 5) and the positive effect of the electron-withdrawing CN group (Scheme 2, **3ba** vs. **3ca**) can support the concerted metalation–deprotonation system.
[15] Recently, a relevant mechanism was proposed in the copper/O_2-promoted oxidative coupling of 1,3-azoles with thiols; S. Ranjit, R. Lee, D. Heryadi, C. Shen, J. Wu, P. Zhang, K.-W. Huang, X. Liu, *J. Org. Chem.* **2011**, *76*, 8999. See the Supporting Information for more details.
[16] When the reaction was carried out in the presence of [D_4]-AcOH, the deuterium incorporation occurred selectively at the indole C2-position (see the following scheme). Thus, a migration of Cu from the C3- into C2-position of the indole would not be involved in the reaction; see: N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125.