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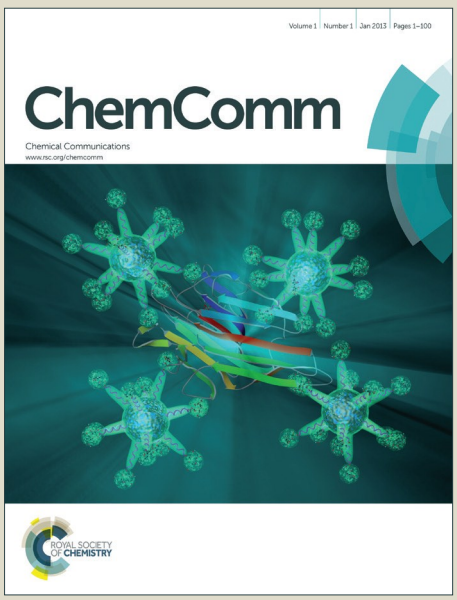

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Copper(II)-mediated regioselective *N*-arylation of pyrroles, indoles, pyrazoles and carbazole *via* dehydrogenative coupling

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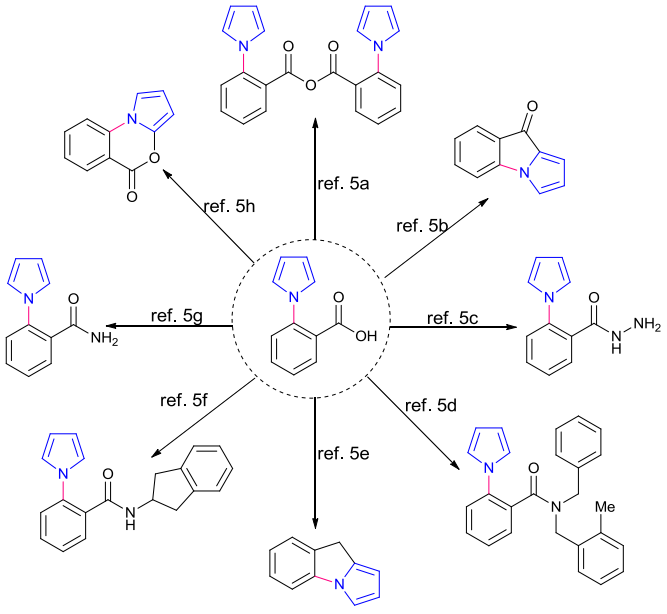
A copper(II)-mediated regioselective *N*-arylation of azoles has been developed using 8-aminoquinoline amide as a directing group. This reaction shows broad substrate scope with different azoles such as pyrroles, indoles, pyrazoles and carbazole with good yields.

C-H Functionalization reactions using directing groups have emerged as more reliable synthetic tools for the regioselective construction of carbon-carbon and carbon-heteroatom bonds.[1,2] Among them, the formation of C-N bonds[3] has attracted considerable attention due to their presence in numerous compounds that are important in biological and pharmaceutical sciences. In particular, *N*-arylated azoles serve as versatile building blocks for the construction of nitrogen-containing structural scaffolds that exhibit interesting medicinal properties (Scheme 1).[4,5] Commonly, they are prepared by the cross-coupling[6,7] of azoles with aryl halides,[8] aryl boronic acids,[9] aryl bismuths[10] and aryl lead reagents.[11] Recently, Patureau and co-workers reported a cross-dehydrogenative coupling approach for the *ortho*-selective amination of diaryl amines with carbazole using Ru as the catalyst and $Cu(OAc)_2$ as the oxidant at 150 °C (Scheme 2a).[12] In this context, the development of new synthetic routes using inexpensive metal source[13] with broad range of nitrogen heterocycles is highly desirable. Herein, we report an efficient copper(II) acetate mediated *ortho*-selective dehydrogenative C-N cross-coupling of arenes with pyrroles, indoles, pyrazoles and carbazole using a removable amide as a directing group (Scheme 2b), This protocol is simple, general and effective at moderate temperature (70 °C) with good yields.

First, we commenced the optimization studies with *N*-(quinolin-8-yl)benzamide **1a** and pyrrole as the model substrates using different bases, solvents and varied amounts of $Cu(OAc)_2$ (Table 1). Gratifingly, the amination selectively occurred at the *ortho*-position to give the target product **2a** in 34% yield when the substrates were stirred with 1 equiv of $Cu(OAc)_2$ at 70 °C in the presence of K_2CO_3 in DMSO (entry 1). The use of Cs_2CO_3 as the base led to an increase in the yield to 44% (entry 3), while Na_2CO_3 afforded inferior results (entry 2). Subsequent screening of the solvents led to an increase in the yield to 51% using DMF, whereas NMP, *i*PrOH and 1,4-dioxane were not effective (entries 4-7). Increasing the amount of $Cu(OAc)_2$ (1.5 equiv) and pyrrole (3 equiv) led to the further enhancement in the yield to 79% (entries 8-11). Similar results were observed using oxygen atmosphere in place of air (entry 12-13). Recrystallization of **2a** in CH_3CN gave single crystal whose structure was determined by X-ray analysis (see Supporting Information). A control experiment confirmed that without $Cu(OAc)_2$ the formation of **2a** was not observed and the starting material was recovered intact (entry 14).



Scheme 1 For some examples of the utilities of 2-(1H-pyrrol-1-yl)benzoic acid

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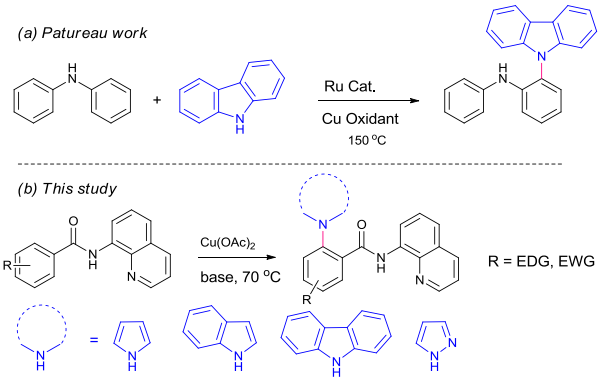
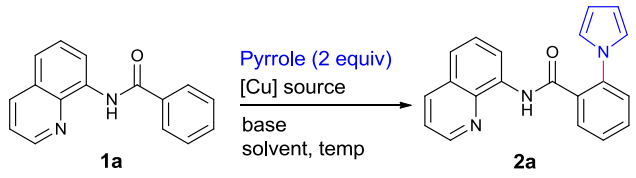
Electronic Supplementary Information (ESI) available:. Supporting information for this article having experimental procedure, crystal structure and data of 2a, characterization data and NMR spectra (^1H and ^{13}C) of **2a-m**, **3a-j**, **4a-b**, **5** and **7** is given via a link at the end of the document.See DOI: 10.1039/x0xx00000x



Scheme 2 *N*-Arylation of azoles via dehdyrogenative cross-coupling

Table 1 Optimization of the reaction conditions

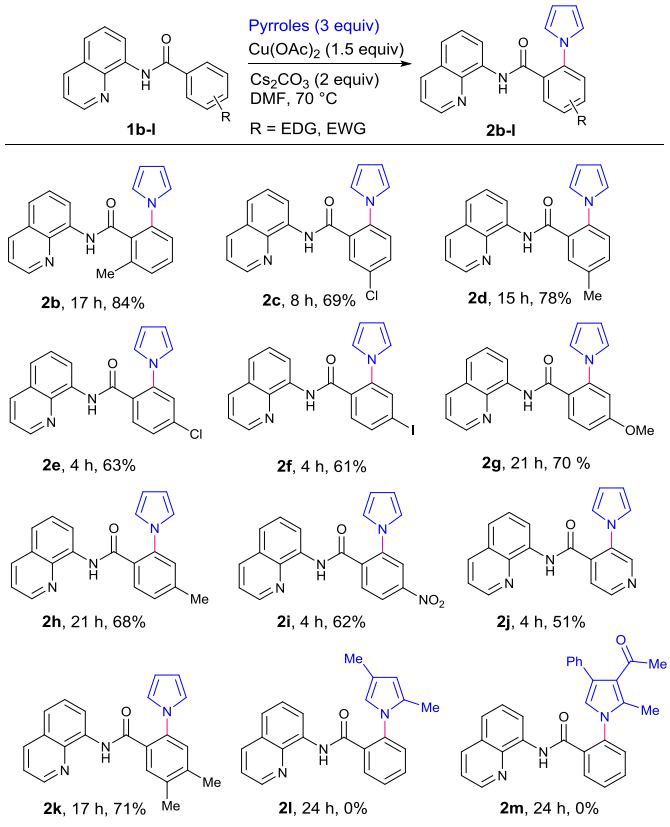


Entry	[Cu] (equiv)	Base	Solvent	Yield (%)[a,b]
1	$Cu(OAc)_2$ (1)	K_2CO_3	DMSO	34
2	$Cu(OAc)_2$ (1)	Na_2CO_3	DMSO	trace
3	$Cu(OAc)_2$ (1)	Cs_2CO_3	DMSO	44
4	$Cu(OAc)_2$ (1)	Cs_2CO_3	NMP	10
5	$Cu(OAc)_2$ (1)	Cs_2CO_3	*i*PrOH	trace
6	$Cu(OAc)_2$ (1)	Cs_2CO_3	1,4-dioxane	0
7	$Cu(OAc)_2$ (1)	Cs_2CO_3	DMF	51
8	$Cu(OAc)_2$ (1.5)	Cs_2CO_3	DMF	71
9	$Cu(OAc)_2$ (2.0)	Cs_2CO_3	DMF	70
10[c]	$Cu(OAc)_2$ (1.5)	Cs_2CO_3	DMF	64
11[d]	$Cu(OAc)_2$ (1.5)	Cs_2CO_3	DMF	79
12[e]	$Cu(OAc)_2$ (1.0)	Cs_2CO_3	DMF	50
13[e]	$Cu(OAc)_2$ (0.2)	Cs_2CO_3	DMF	18
14	-	Cs_2CO_3	DMF	0

[a] Reaction conditions: *N*-(quinolin-8-yl)benzamide **1a** (0.2 mmol), $Cu(OAc)_2$, pyrrole (0.4 mmol), base (0.4 mmol), solvent (1 mL), 70 °C, 21 h. [b] Isolated yield. [c] Pyrrole (0.3 mmol) was used. [d] Pyrrole (0.6 mmol) was used. [e] Using O_2 balloon.

Having the optimal conditions in hand, we sought to further explore the reaction scope with a broad range of *N*-(quinolin-8-yl)benzamide derivatives (Scheme 3). The substrates **1b** having 2-Me substituent underwent the reaction to produce the target product **2b** in 84% yield. The substrates **1c-d** bearing 3-Cl and 3-Me functionalities readily reacted to afford the desired products **2c** and **2d** in 69 and 78% yields, respectively, while **1e-i** bearing electron donating and electron-withdrawing groups in the *para* position proceeded reaction smoothly to provide the corresponding *ortho*-aminated products **2e-i** in 61-70% yields. Heterocyclic compound, isonicotinamide **1j** underwent reaction to give the aminated product **2j** in 51% yield, whereas the reaction of 3,4-diMe substituted substrate **1k** produced the target product **2k** in 71% yield. However, the substrate **1a** with substituted pyrroles, 2,4-dimethylpyrrole and 1-(2-methyl-4-phenyl-1*H*-pyrrol-3-yl)ethan-1-one, failed to produce the desired **2l** and **2m**, which might be due to the steric hindrance of the substituents present in the pyrroles. These results suggest that the protocol is compatible with the substrates bearing substitution at *ortho*, *meta* as well as *para* positions. Furthermore, the substrates with electron withdrawing group **2i** exhibit greater reactivity compared to that having electron donating group **2g**. In addition, the substrates having halides such as chlorine **2c**, **2e** and iodine **2i** are tolerated under these reaction conditions.

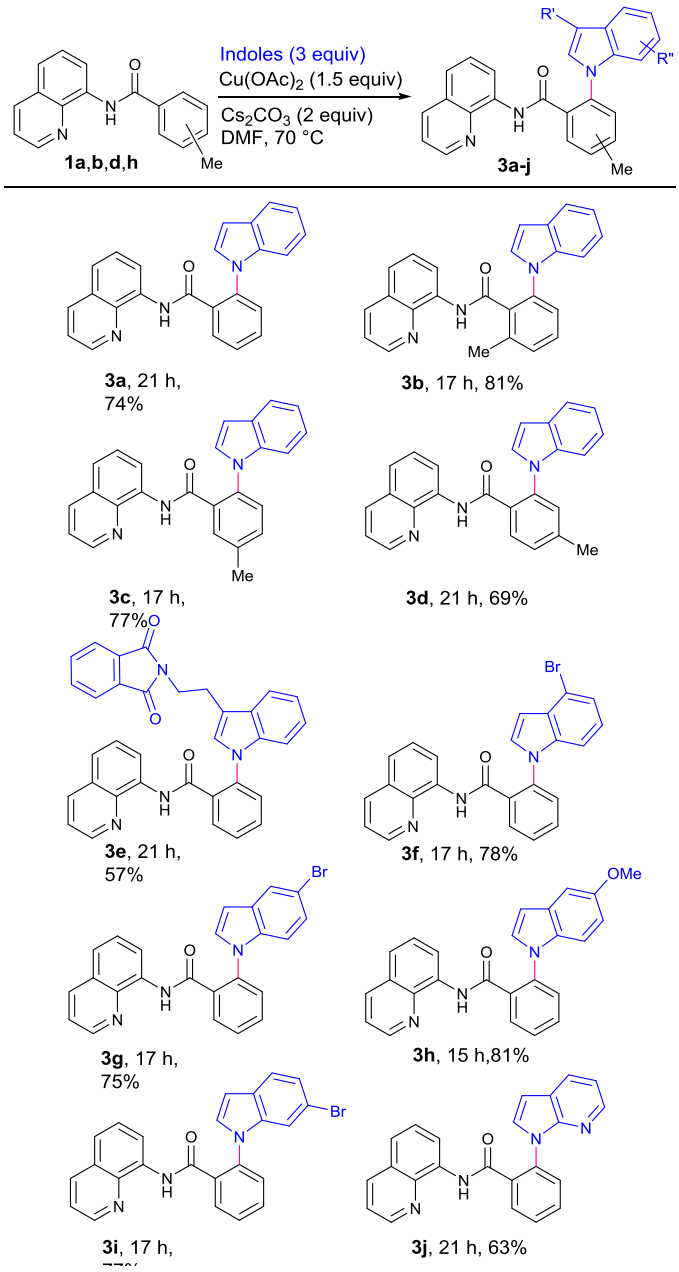
Next, the scope of the reaction was extended to the *N*-arylation of indoles with 8-aminoquinoline amides (Scheme 4). The reactions proceeded efficiently in high yields. For examples, *N*-(quinolin-8-yl)benzamide **1a** underwent reaction to furnish the target *ortho*-aminated product **3a** in 74% yield. In addition, the reaction of the substrates **1b**, **1d** and **1h** with methyl substituent at *ortho*, *meta* and *para*-positions produced the corresponding aminated compounds **3b**-**d** with 69-81% yields. Furthermore, the substrate **1a** with the substituted indole, 2-(2-(1*H*-Indol-3-yl)ethyl)isoindoline-1,3-dione, furnished **3e** in 57% yield. Similarly, the reactions of **1a** with the indoles bearing 4-bromo, 5-bromo, 5-methoxy and 6-bromo substituents afforded the corresponding cross-coupled products **3f-i** in 75-81% yields, while azaindole underwent reaction to produce **3j** in 63% yield.



Scheme 3 Substrate scope of N-(quinolin-8-yl)benzamides with pyrrole.[a,b] a Reaction conditions: N-(quinolin-8-yl)benzamide 1a (0.2 mmol), $Cu(OAc)_2$ (0.3 mmol), pyrrole (0.6 mmol), Cs_2CO_3 (0.4 mmol), DMF (1 mL), 70 °C. [b] Isolated yield.

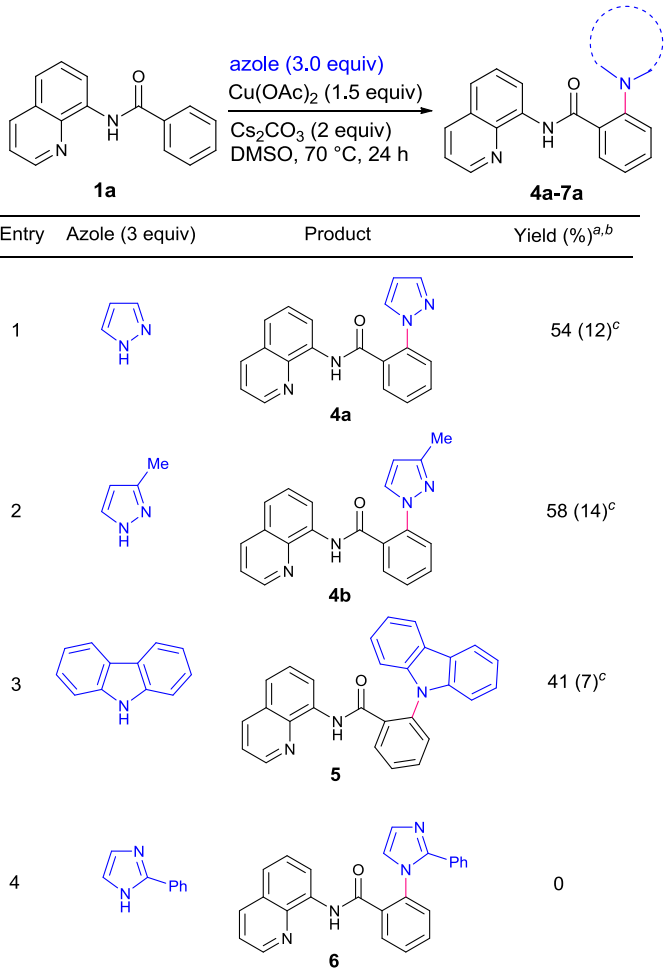
Furthermore, we explored the scope of the procedure for the reactions of different azoles with *N*-(quinolin-8-yl)benzamide **1a** as

the representative example (Scheme 5). These reactions exhibited superior results employing DMSO as the solvent compared to that of DMF. For examples, pyrazole underwent reaction to produce the target product **4a** in 54% yield. Similar result was observed with 3-methylpyrazole leading to the formation of **4b** in 58% yield. In addition, the reaction of carbazole furnished the desired cross-coupled product **5** in 41% yield. However, 2-phenylimidazole failed react to yield **6** and the starting materials were recovered.

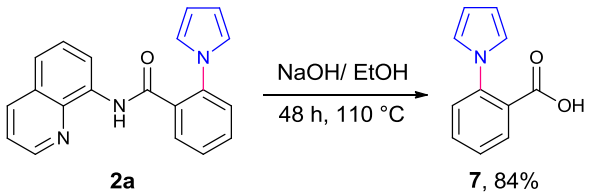


Scheme 4 Substrate scope of *N*-(quinolin-8-yl)benzamides with indoles.[a,b] [a] Reaction conditions: *N*-(quinolin-8-yl)benzamide 1a (0.2 mmol), $Cu(OAc)_2$ (0.3 mmol), indole (0.6 mmol), Cs_2CO_3 (0.4 mmol), DMF (1 mL), 70 °C. [b] Isolated yield.

Finally, the removal of the directing group was studied using compound **2a** as the representative example (Scheme 6).[13e] The compound **2a** underwent readily hydrolysis with NaOH in ethanol at 110 °C to afford 2-(1*H*-pyrrol-1-yl) benzoic acid **7** in 84% yield, which is a key intermediate for the construction of diverse nitrogen containing structural frameworks as described in Scheme 1.[5]

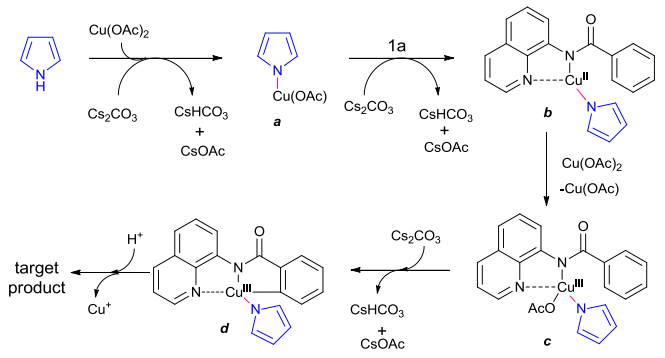


Scheme 5 Substrate scope of *N*-(quinolin-8-yl)benzamide **1a** with different azoles.[a-c] [a] Reaction conditions: *N*-(quinolin-8-yl)benzamide **1a** (0.2 mmol), $Cu(OAc)_2$ (0.3 mmol), azole (0.6 mmol), Cs_2CO_3 (0.4 mmol), DMSO (1 mL), 70 °C, 24 h. [b] Isolated yield. [c] Using DMF.



Scheme 6. Directing group removal

The proposed reaction pathway is shown in Scheme 7. In the presence of base, azole may undergo reaction with $Cu(OAc)_2$ to produce copper(II) species ***a***,[14] which may react with the substrate **1a** via ligand exchange to give copper(II) intermediate ***b***. $Cu(OAc)_2$-mediated oxidation of ***b*** may lead to the formation of copper(III) species ***c***. Intramolecular C-H cupration of the aryl ring may give the intermediate ***d***, which can provide the target product by reductive elimination followed by protonation. This proposed reaction pathway also explains the necessity of excess $Cu(OAc)_2$ and base to realize the products in good yields.



Scheme 7. Proposed reaction pathway

In summary, we have developed an efficient copper-mediated 8-aminoquinoline amide directed *N*-arylation of pyrroles, indoles, pyrazoles and carbazole *via* intermolecular cross-dehydrogenative coupling reaction. This protocol exhibits broad substrate scope and high functional group tolerance, which may open a new avenue for further development of dehydrogenative coupling protocols for the coupling azoles with hydrocarbons.

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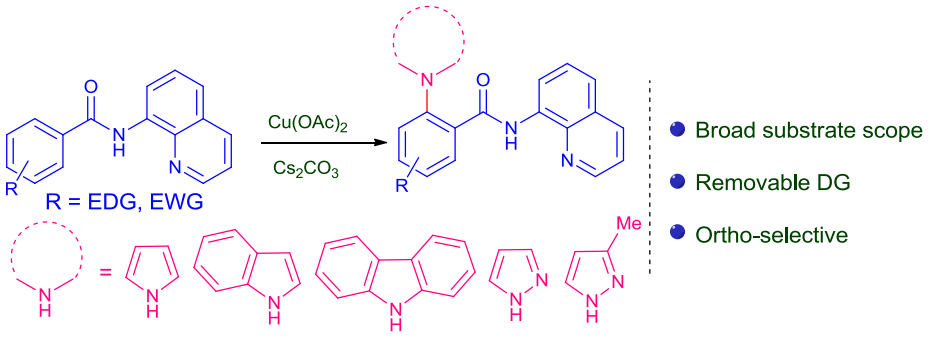
Graphical Abstract



Copper-mediated regioselective *N*-arylation of pyrroles, indoles, pyrazoles and carbazole is described using 8-aminoquinoline amide as a directing group via dehydrogenative coupling. The protocol has broad substrate scope with good yields at moderate temperature.