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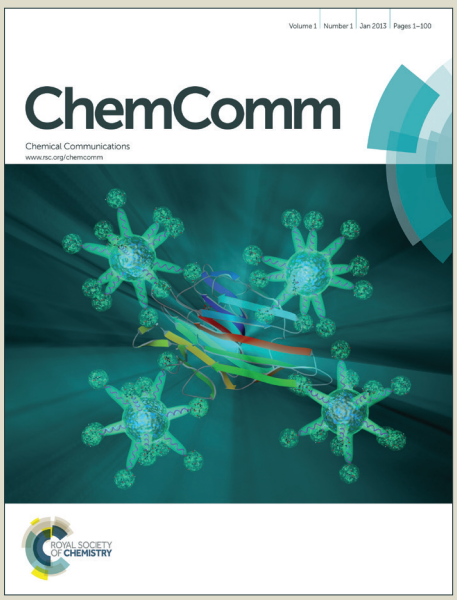

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ARTICLE TYPE

Ligand –Promoted Intramolecular Dehydrogenative Cross-Coupling with Cu Catalyst: A Direct Access to Polycyclic Heteroarenes

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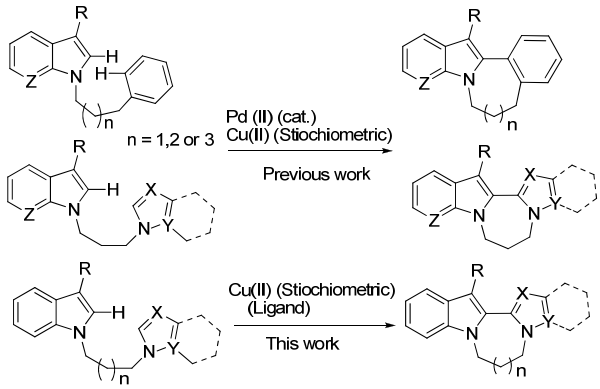
A copper (II)-promoted intramolecular C-H coupling reaction between indole-2 and imidazole-2 moiety, for polycyclic heteroarenes synthesis has been developed. The method provides direct access to biheteroaryl incorporated polycyclic frameworks, which are of huge interest in the area of functional materials and drug-discovery.

Apart from the traditional C−C bond formation reactions, transition-metal catalyzed C-H cross coupling reactions have emerged as one of the most important methodologies in modern organic chemistry.[1]The importance lies in the fact that the mandatory pre-functionalization of substrates can be avoided when using two activated C-H bonds as coupling partners. Such direct couplings of the C-H bonds not only have an added advantage in terms of generating minimal waste product but also offer an economical route for targeted molecule synthesis. Although synthetically very attractive, most of the C-H activation protocols suffer from limited substrate scope and site selectivity.[2]

The majority of C−H functionalization processes including intermolecular and intramolecular cross-couplings[3] are limited to the use of expensive noble metals such as Pd, Rh, or Ir as catalysts,[4] and the development of cheaper metal catalyst is extremely desirable. In this context, the use of Cu as a catalyst can be an attractive alternative owing to the low cost, less toxicity and ease in isolation. However, its low reactivity towards direct activation of C-H bonds limits its application. Thus, the ability to prepare synthetically relevant scaffolds *via* C−H activation with Cu catalysts would be of significant importance.

Very recently, the use of palladium catalysts have shown to facilitate the oxidative intermolecular C-H/C-H cross-coupling of *p*-electron-rich thiophenes, furans, indoles and pyrroles with various important classes of heteroarenes such as xanthines, azoles, and indolizines, pyridine N-oxides.[6,7] Ofial and co-workers reported an efficient palladium-catalyzed dehydrogenative cross-coupling of a benzoazole (i.e., benzothiazole and benzimidazole) with an azole.[8] Recent seminal reports on the carbonyl-directed oxidative C−H arylation and alkenylation reactions have led to the development of a powerful synthetic methodology for producing both bis-arenes and vinylarenes.[9] The metal-ligand chelate-assisted catalytic oxidative C−H coupling methods have been utilized for intramolecular annulation of arene compounds in forming benzofurans[10] as well as for lactone and lactam products.[11] The strategy has also been used for the synthesis of biologically active complex organic molecules.[12] Although, Greaney and coworkers reported the synthesis of medium sized ring (mainly 7 and 8 membered rings)



Scheme 1: Intramolecular cross-coupling for biheteroaryl ring formation

through Pd-catalyzed intramolecular C-H activation,[13] to the best of our knowledge, the development of C(sp^2)−H/ C(sp^2)−H dehydrogenative coupling annulation reactions of heteroaryl systems for the synthesis of embedded six membered ring system using Cu catalysts remains unexplored.

Herein, we report a ligand assisted Cu-catalyzed direct C-H bond activations followed by C-C bond formation in heteroarenes, which might prove its applicability in the synthesis of related natural products in the near future (Scheme 1). Various reports for the intermolecular C(sp^2)-H activation suggests that a

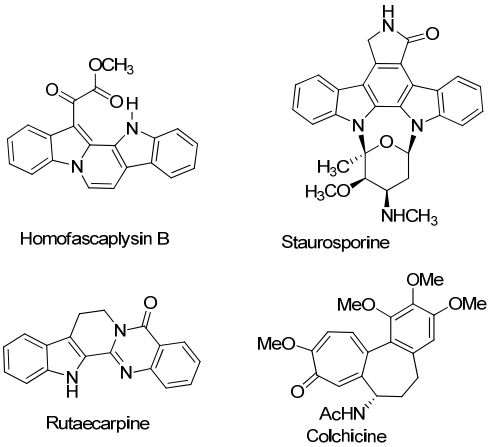


Fig. 1: Biologically active natural products with biheteroaryl/ biaryl ring

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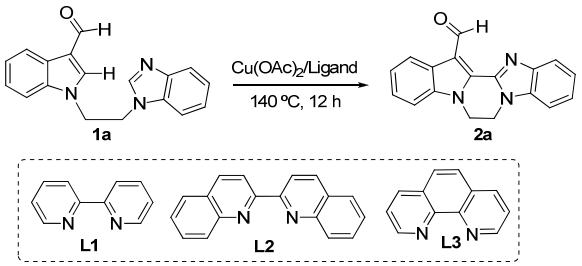
Table 1. Optimization of cross-coupling reaction[a]



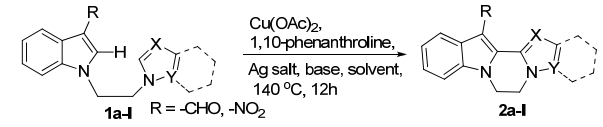
entry	$Cu(OAc)_2$ (equiv)	Ligand (equiv)	Ag (equiv)	Base (equiv)	yield (%)[b]
1	0.1	L1(0.2)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	7
2	0.1	L2(0.2)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	6
3	0.1	L3(0.2)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	21
4	0.2	L3(0.2)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	17
5	0.2	L3(0.4)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	57
6	0.2	L3(0.4)	Ag_2CO_3 (2.0)	Na_2CO_3 (2.0)	55
7	0.2	L3(0.4)	Ag_2CO_3 (2.0)	Li_2CO_3 (2.0)	51
8	0.2	L3(0.4)	Ag_2CO_3 (2.0)	NaOAc (2.0)	41
9	0.2	L3(0.4)	Ag_2CO_3 (2.0)	Li^{t}OBu (2.0)	22
10	0.2	L3(0.4)	Ag_2CO_3 (2.0)	Na^{t}OBu (2.0)	5
11	0.2	L3(0.4)	Ag_2CO_3 (2.0)	K_2CO_3 (0)	20
12	0.2	L3(0.4)	Ag_2CO_3 (0)	K_2CO_3 (2.0)	0
13	0.2	L3(0)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	<5
14	0	L3(0.4)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	0
15	0.5	L3(1.0)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	55
16	1.0	L3(2.0)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	63
17 [c,d]	1.0	L3(2.0)	Ag_2CO_3 (2.0)	K_2CO_3 (2.0)	43 [c], 38 [d]
18	1.0	L3(2.0)	Ag_2CO_3 (0)	K_2CO_3 (2.0)	0
19	2.0	L3(4.0)	Ag_2CO_3 (0)	K_2CO_3 (2.0)	8 + 16 (di)[e]

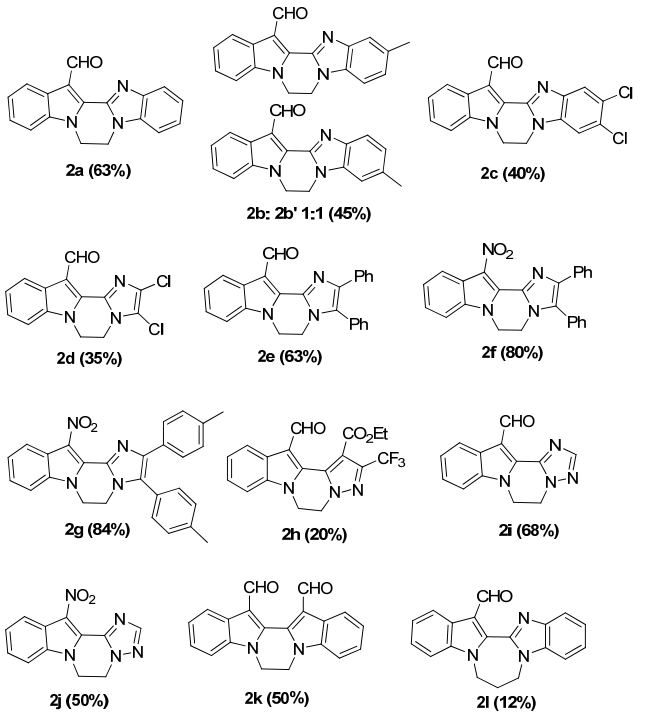
[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), $Cu(OAc)_2$, Ligand, Ag salt and base in xylene (1mL) at 140 °C for 12h. [b]Isolated yields.[c]Reaction was carried out at 140 °C for 24 h. [d]Reaction was carried out at 165 °C for 12 h. [e] Reaction gave both cyclised and 2,2'-azole coupled dimeric product (See SI Scheme S1).

pKa less than 35 is considered to be effective for heteroaryl coupling.[5(a)] Thus, we hypothesized that the pKa of targeted $C(sp^2)$-H for the Cu-catalyzed reaction might be an important factor in dictating the outcome of the reaction and was given importance in selecting the reactants. In this report, the indole system has been considered as one of the substrates, given its reactivity for 2-position C-H bond and its widespread occurrence in biologically active compounds[14] (Fig. 1).

We started our investigations with **1a** as the model substrate and systematically examined the effect of metal catalysts in presence of Ag salts, various ligands, bases and solvents (Table 1). The initial screening started with 0.1 equiv of $Cu(OAc)_2$, 0.2 equiv bipyridine (**L1)**, 2.0 equiv Ag_2CO_3 and 2 equiv of K_2CO_3 at 140 °C for 12h, which afforded 7% of the product **2a** (entry 1). It was observed that while keeping the other parameters constant, when the ligand was changed to **L2,** the yield of **2a** declined**.** Whereas, when 1,10-phenanthroline (**L3**) was used as a ligand, the yield of **2a** enhanced to 21% **t**hus, indicating 1,10-phenanthroline (**L3**) as the most effective among the three ligands (entry 2 and 3). Since most of the Cu-catalyzed C-H/ C-H activation reactions are feasible only at relatively higher temperature, the ligand plays an extremely important role in stabilizing the Cu-catalyst at such high temperatures.[5(a)] Hence, the choice and proportion of appropriate ligand with respect to the metal catalyst is a crucial factor.[5] In this methodology, we observed that keeping the ratio of $Cu(OAc)_2$ to the ligand **L3**

Table 2. Substrate Scope for cross-coupling reaction[a,b]





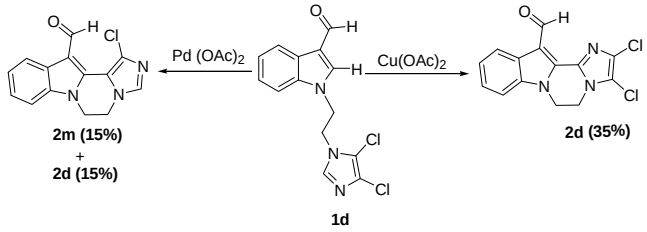
[a]Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), Ligand (**L3**) (0.4 mmol), Ag_2CO_3 (0.4 mmol) and K_2CO_3 (0.4 mmol) in xylene (1mL) at 140 °C for 12h. [b]Isolated yields. [c]Reaction was carried out at 0.18 mmol scale (See SI). [d]Reaction was carried out at 0.37 mmol (See SI).

equal, afforded 17 % of **2a** (entry 4) and increasing the ratio to 1:2 enhanced the yield to 57% (entry 5).

Changing the base to Na_2CO_3 and Li_2CO_3 did not have much effect on the reaction yield. However, increasing the basicity decreased the yield of **2a** drastically (entry 6-10). Eliminating the base from reaction mixture afforded only 20% of desired product (entry 11). The ligand phenanthroline (**L3**) and Ag_2CO_3 was important for initiating the reaction (entry 12 and 13), while the reaction failed to proceed in the absence of Cu-catalyst (entry 14). Increasing the amount of $Cu(OAc)_2$ from 0.2 equiv to 0.5 equiv in the presence of 1 equiv of 1,10-phenanthroline, 2 equiv Ag_2CO_3 and K_2CO_3 did not have much pronounced effect on the yield (entry 15). However, when the amount was further increased to 1 equiv of $Cu(OAc)_2$ and 2 equiv of **L3**, under similar conditions, the yield of **2a** improved to 63% (entry 16). Increase in either the reaction time from 12 h to 24 h or the reaction temperature from 140 °C to 165 °C, reduced the yield of the product to 43 and 38% (entry 17) respectively. When the reaction was carried out in the absence of Ag salt, the reaction failed to proceed (entry 18). However, increasing the $Cu(OAc)_2$ loading to 2.0 equivalent in absence of silver salt showed some reactivity (8% yield). It was found that when **1a** was treated with 2 equivalents of $Cu(OAc)_2$, 4 equivalents of 1,10-phenanthroline and 2 equivalents of potassium carbonate gave 8% of **2a** and 16%

of 2,2'-azole coupled dimeric product (entry 19). These results clearly indicate the importance of copper for the C-H activation step.

With the optimized reaction condition in hand (entry 16), the utility of the newly developed methodology of Cu-catalyzed intramolecular cross-dehydrogenative coupling was examined. We proceeded mainly with the heterocyclic ring systems, with an aim of synthesizing novel heterobiaryl annulated in a six-membered ring. All the substrates were synthesized *via N*-alkylation of either 3-substituted indole with the corresponding 1-(2-haloethyl)-1H-azole derivatives or the substituted azoles with 3-substituted 1-(2-haloethyl)-1H-indole derivatives. A mixture of inseparable isomers **2b: 2b'** (46%) in 1:1 ratio was obtained when the corresponding substrate (inseparable mixture of **1b** and **1b'**) was subjected to the optimized reaction condition. Further, the N-alkylated derivative of 5,6-dichlorobenzimidazole was chosen as substrate in order to assess the tolerance of -Cl group towards Cu-catalyzed C-H activation. The reaction afforded 40% of the desired cyclized product (**2c**) keeping the –Cl groups intact.



Scheme 2: Dehydrogenative cross-coupling of **1d** in presence of Pd and Cu

We next studied the N-alkylated 4,5-dichloroimidazole **1d** as a viable substrate, since, there exists a possibility for competitive occurrence of C-H versus C-Cl activation, both leading to different cyclized products. The reaction was performed using both Pd and Cu-catalyst. Interestingly, while Cu- catalyst solely afforded the C-H activated product (**2d**) in 35% yield, the Pd-catalyst[13], produced a 1:1 mixture of C-H and C-Cl activated products (**2d** and **2m**) in 30% yield (Scheme 2).

We focused our efforts on studying the substrate scope of the reaction further on 4,5 aryl substituted imidazoles and found that most of the substrates screened were reactive towards the developed dehydrogenative cyclization (Table 2). The wide functional group tolerance of the method was nicely demonstrated by the fact that aldehyde, nitro, and ester groups were all well tolerated, giving access to the cyclized products in moderate to good yields **2**(**a-l**). The halide substitution was also tolerated thus leaving ample opportunities for further functionalization *via* conventional cross-coupling techniques.

When the 4,-5 dichloro imidazole was replaced with 4,5-diphenyl, the yield of desired product increased to 63% (**2e**). Further change in substituent at 3-position of indole from aldehyde to nitro increased the yield of the reaction to 80% (**2f**) . The replacement of diphenyl imidazole moiety with ditolyl imidazole in N-alkylated 3-Nitroindole afforded a highest yield of 84% of the desired C-H activated product (**2g**). The incorporation of electron withdrawing trifluoromethane and ester groups in N-alkylated pyrazole reduced the yield of the desired product (**2h**) drastically. In contrast the yield was considerably improved on incorporation of N-substituted 1,2,4-triazole derivatives (**2i** and **2j**). When the azole system was replaced with indole-3-carboxaldehyde, a six membered dialdehyde product (**2h**) was obtained in 50% yield. Homologation of the chain of substrate **1a** resulted in decreased yield of the 7- membered ring product (**2l**). The intramolecular C-H activated cyclization was also confirmed by the X-ray crystallographic structure of Compound **2h**(Fig. 2).

In order to investigate the synthetic potential of the cyclized product **2a**, various routine transformations were performed. Allylation[15] and nitromethylation[16] of **2a** provided the corresponding product in 76% and 95% yield respectively, whereas *p*-bromophenyl hydrazine condensation afforded the hydrazone derivative in 90% yield (Scheme S2 in supporting information).[17]

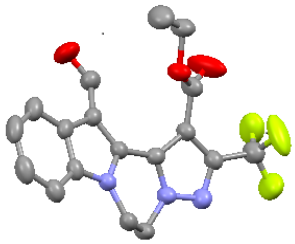
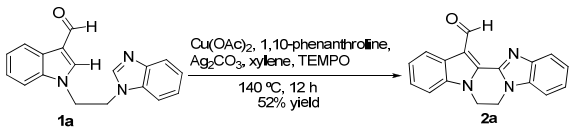
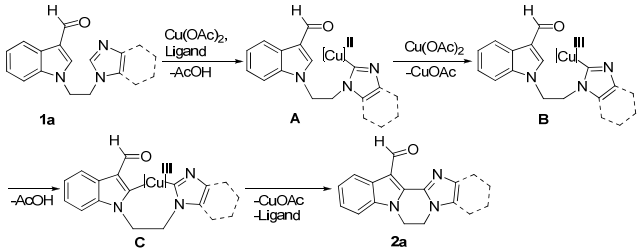


Fig. 2: X-ray crystallographic structure of **2h**



Scheme 3: The effect of TEMPO on cyclization reaction



Scheme 4: Plausible pathway of the cyclization reaction

To gain some mechanistic insight into the reaction, we conducted a dehydrogenative cross-coupling reaction in presence of radical quencher 2,2,6,6-tetramethyl piperidine-*N*-oxyl (TEMPO). The yield of the coupled product did not change significantly and no side product was observed. Thus, the possibility of a radical pathway can be ruled out (Scheme 3). We carried out some intra- and intermolecular coupling reactions to understand the preference for the initial site of C-H bond activation (indole *vs* benzimidazole). Based on our data (Scheme S3 in supporting information) and literature precedence, we propose that first, copper and 1,10-phenanthroline form a neutral doubly N,N-chelated complex. The complex then proceeded for acetate-ligand mediated cuperation of the 1,3-azole moiety[18,19] generating corresponding heteroarylcopper (II) intermediate **A**.[20] Further disproportionation of copper in azolylcopper A generates complex **B**, which prompts C-H cuperation of the indole moiety yielding organocopper (III) complex **C**. On subsequent reductive elimination of **C** generates the desired cyclized product **2a** (Scheme 4).

In conclusion, we have developed an efficient method for the synthesis of a series of polyheterocyclic arenes *via* copper-

catalyzed intramolecular cross dehydrogenative coupling (CDC) reactions. The CDC has easily yielded the biheteroaryl systems with embedded six membered ring. The developed method shows high experimental simplicity and functional group compatibility.

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