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# Functional 1,8-naphthyridine copper(I) complex as efficient catalyst for *n*-arylation of imidazoles coupling reactions

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The functional 1,8-naphthyridine copper(I) complex, synthesized through a non-catalyst C($sp^3$)–H methylenation, catalyzes the cross-coupling reaction of aryl halides with imidazoles, by C—N bond formation. The Cu(I) complex catalyzes the reaction with a low catalyst loading (1%, molar fraction) and cheap base even under aerobic conditions. The procedure tolerates aryl halides with various functional groups (such as methyl, methoxy, acetyl, fluoro, nitrile and nitro groups) and gives the corresponding coupling products in moderate to high yields.

**Keywords:** Catalysts, Cross-coupling reactions, N-Arylation, Copper(I) complex, Imidazoles,

Naphthyridines (pyridopyridines, diazanaphthalenes) represent a group of six isomeric heterocyclic systems containing two fused pyridine rings with different mutual arrangements of nitrogen atoms[1,2]. Of the six isomeric pyridopyridines, 1,8-naphthyridine derivatives have been studied the most during the last 20 years[3]. Among these, 1,8-naphthyridine scaffolds are interesting synthetic targets because these compounds possess a wide spectrum of biological activities, including antibacterial, anti-inflammatory, antitumor, antimalarial, antiproliferative, antihypertensive, and antioxidant activities[4-6]. Additionally, some 1,8-naphthyridine derivatives have been designed and developed as fluorescent dyes, and sensors because of their outstanding optical properties[7].

N-aryl imidazoles are key structural motifs in a wide range of agrochemicals, pharmaceuticals, and biologically active compounds[8,9]. Recently, Buchwald *et al.*[10] and Taillefer *et al.*[11] found that several N- and O-based ligands could greatly facilitate the copper-catalyzed path for the N-arylation of imidazoles. However, this method suffers from some limitations, such as the high stoichiometric consumption of copper reagent or ligand (usually 20%, molar fraction) and longer reaction time (generally required 24–72 h)[12-14].

We have earlier reported the synthesis of two methylene bridged 1,8-naphthyridine ligands and copper(I) complex through a non-catalyst C($sp^3$)–H methylenation (Fig. 1), and studied their spectroscopic properties by theoretical calculations[15]. To the best of our knowledge, there is no report of a 1,8-naphthyridine copper catalyst used for C–N cross-coupling reaction. We report herein the first application of N-arylation of imidazoles directly catalyzed by the copper(I) complex reported earlier[15].

## Experimental

All the reagents were purchased from commercial suppliers and used without further purification. The functional 1,8-naphthyridine copper(I) complex (C1) was synthesized according to the reported method[15]. Briefly, first the ligand was synthesized as follows: To a 50 mL flask, were added 7-acetamino-2, 4-dimethyl-1,8-naphthyridine (100 mg, 0.46 mmol), 2-carboxybenzaldehyde (84 mg, 0.56 mmol), and 40 mL of freshly distilled *N*,*N*-dimethylformamide. The mixture was heated with stirring for 24 h at 150 °C under nitrogen atomsphere. After cooling to room temperature, the mixture was removed under reduced pressure to obtain a pale yellow solid. The crude product was purified by chromatography on silica gel (ethyl acetate:petroleum ether = 1:1) to give the ligand (105 mg, Yield: 65%). For synthesis of the copper(I) complex (C1), the ligand (0.072 g, 0.2 mmol) and CuI (158 mg, 0.8 mmol) were mixed with stirring in dichloromethane (25 mL) under a nitrogen atmosphere at room temperature for 24 h. The resulting solution was filtered and the solvent was removed *in vacuo* to yield a yellow precipitate. Yield: (65 mg, Yield: 36%).

For the catalysis reaction, the catalyst C1 (12 mg, 0.01 mmol), imidazole (1.0 mmol), aryl halide (1.0 mmol), NaOH (80 mg, 2.0 mmol), and dimethyl sulfoxide (DMSO, 5 mL) were taken in a sealed tube.

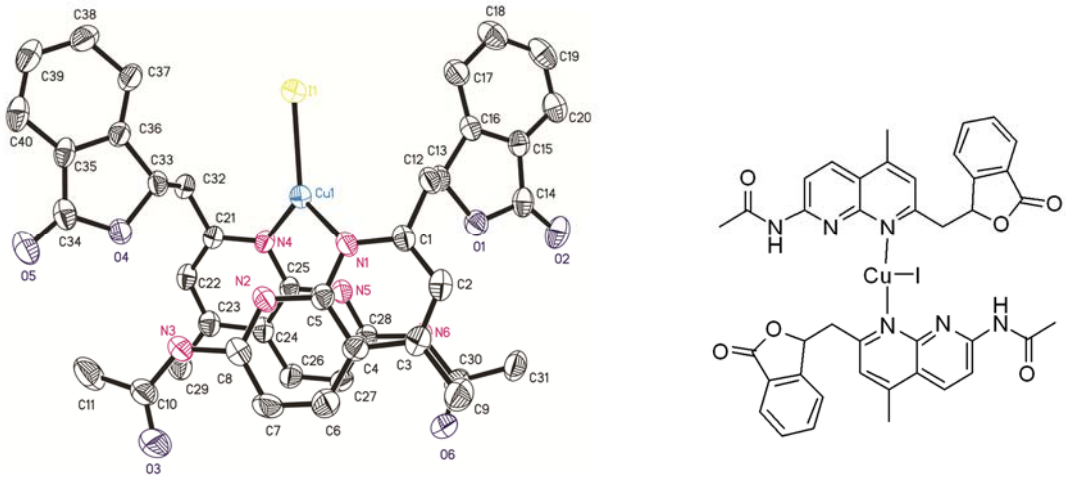


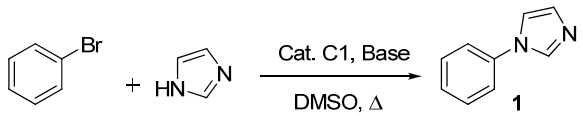

Fig. 1 — Structure of functional 1,8-naphthyridine copper (I) complex (C1)[15].

The reaction mixture was stirred at 100 °C for 4 h and then cooled to room temperature. After adding 5 mL of $H_2O$, the solution was extracted with ethyl acetate. The organic layer was then dried over anhydrous $Na_2SO_4$ and the solvent was removed under reduced pressure. The N-arylated product was finally obtained by column chromatography on silica gel.

## Results and discussion

We first focused on the N-arylation of imidazole, since 1-arylimidazoles are important motifs found in a series of medicinally important compounds that have been exploited as key building blocks for the synthesis of N-heterocyclic carbenes[16-18]. As shown in Table 1, among the different bases tested in the catalysis under the same reaction conditions, NaOH gave the best isolated yield of around 95% and KOH gave the second isolated yield of around 93% after reaction for 4 h (Table 1, Entry 1 and 2). Other inorganic bases, including $Na_2CO_3$, $K_2CO_3$ and $Cs_2CO_3$ were less effective than NaOH requiring a longer reaction time of 12 h (Table 1, Entry 3-5). However, only a trace amount of product was found when organic bases such as triethylamine or pyridine, were used (Table 1, Entries 6 and 7). Solvent is another important factor affecting the catalysis. DMSO was highly efficient as a solvent, giving the product in a yield of 95%. Further, a low temperature slowed the reaction rate. Only a yield of 80% was obtained when the reaction was carried out at 80 °C (Table 1, Entry 12). Furthermore, investigation revealed that 4 h was enough for the reaction to go to completion. When the reaction time was decreased to 2 h, the yield dropped to 62% (Table 1, Entry 14), and when the reaction time was lengthened to 6 h, the yield was still only 95%

Table 1 — Reaction conditions for functional 1,8-naphthyridine copper(I) complex **C1** catalyzed N-arylation of imidazole with bromobenzene[a]



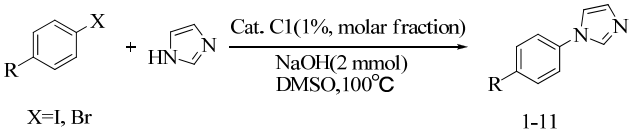

| Entry | Base | Solvent | Time (h) | Temp. (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | NaOH | DMSO | 4 | 100 | 95 |
| 2 | KOH | DMSO | 4 | 100 | 93 |
| 3 | $K_2CO_3$ | DMSO | 12 | 100 | 52 |
| 4 | $Na_2CO_3$ | DMSO | 12 | 100 | 56 |
| 5 | $Cs_2CO_3$ | DMSO | 12 | 100 | 65 |
| 6 | $Et_3N$ | DMSO | 24 | 100 | <10 |
| 7 | Pyridine | DMSO | 24 | 100 | <10 |
| 8 | NaOH | DMF | 4 | 100 | 87 |
| 9 | NaOH | Toluene | 12 | 110 | 78 |
| 10 | NaOH | Xylene | 12 | 110 | 80 |
| 11 | NaOH | THF | 12 | 80 | 25 |
| 12 | NaOH | DMSO | 4 | 80 | 80 |
| 13 | NaOH | DMSO | 6 | 100 | 95 |
| 14 | NaOH | DMSO | 2 | 100 | 62 |
| 15[c] | NaOH | DMSO | 4 | 100 | 75 |

[a]React. cond.: bromobenzene (1.0 mmol), imidazole (1.0 mmol), base (2.0 mmol), complex **C1** (0.01 mmol), solvent (5 mL), air atmosphere; [b]isolated yield; [c]0.5% (molar fraction) catalyst.

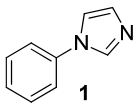
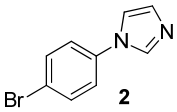
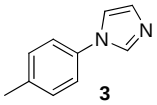
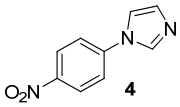
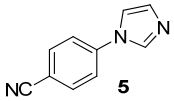
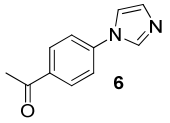
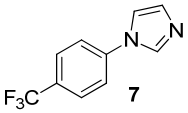
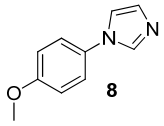
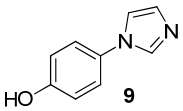
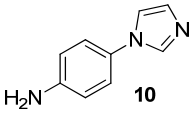
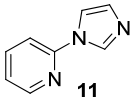
(Table 1, Entry 13). Reducing the loading of the catalyst to 0.5% (molar fraction) caused the reaction yield to drop to 75% (Table 1, Entry 15).

Under the above optimal reaction conditions, a broader study was undertaken. The coupling reactions of imidazole with substituted aryl iodides and bromides were tested. Table 2 shows that generally the

Table 2 — N-arylation of imidazole with different aryl halides catalyzed by complex **C1**

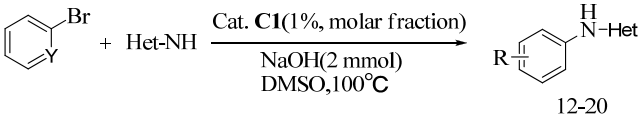



X=I, Br 1-11

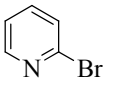
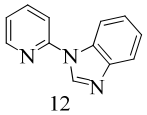
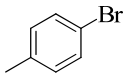
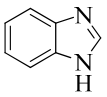
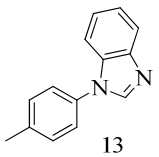
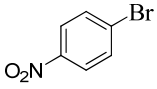
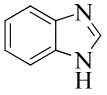
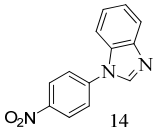
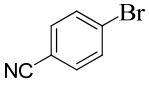
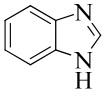
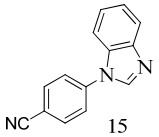
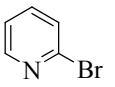
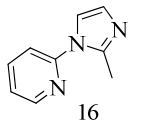
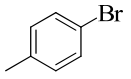
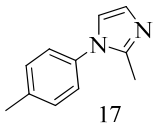
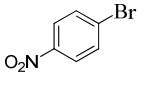
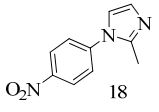
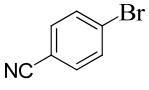
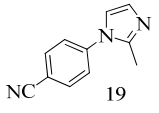
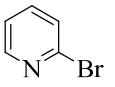
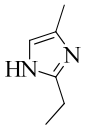
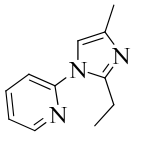
| Entry | Aryl halide | Product | Yield[b](%) |
|---|---|---|---|
| 1 | X=I, R=H |  **1** | 98 |
| 2 | X=Br, R=H | | 95 |
| 3 | X=I, R=Br |  **2** | 94 |
| 4 | X=Br, R= Br | | 81 |
| 5 | X=I, R=$CH_3$ |  **3** | 96 |
| 6 | X=Br, R=$CH_3$ | | 88 |
| 7 | X=I, R=$NO_2$ |  **4** | 91 |
| 8 | X=Br, R=$NO_2$ | | 86 |
| 9 | X=I, R=CN |  **5** | 93 |
| 10 | X=Br, R=CN | | 88 |
| 11 | X=Br, R=$COCH_3$ |  **6** | 90 |
| 12 | X=Br, R=$CF_3$ |  **7** | 90 |
| 13 | X=Br, R=$OCH_3$ |  **8** | 94 |
| 14 | X=Br, R=OH |  **9** | 95 |
| 15 | X=Br, R=$NH_2$ |  **10** | 88 |
| 16[c] | X=Br, R=H |  **11** | 90 |

[a]React. cond.: aryl halide (1.0 mmol), imidazole (1.0 mmol), NaOH (2.0 mmol), complex **C1** (0.01 mmol), DMSO (3 mL) at 100 °C in air; [b]isolated yields; [c]aryl halide: 2-bromopyridine.

Table 3 — Complex **C1** catalyzed N-arylation of aryl halides with other imidazoles[a]




12-20

| Entry | Aryl halide | Het-NH | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  12 | 90 |
| 2 |  |  |  13 | 80 |
| 3 |  |  |  14 | 85 |
| 4 |  |  |  15 | 88 |
| 5 |  |  |  16 | 86 |
| 6 |  |  |  17 | 76 |
| 7 |  |  |  18 | 80 |
| 8 |  |  |  19 | 82 |
| 9 |  |  |  20 | 70 |

[a]React. cond.: aryl bromide (1.0 mmol), imidazole derivative (1.0 mmol), NaOH (2.0 mmol), complex **C1** (0.01 mmol), DMSO (3 mL) at 100 °C in air; [b]Isolated yields.

substituted aryl iodides resulted in higher yields compared to the substituted aryl bromides under the same reaction conditions (products 1-5)[19-22]. It is satisfying that moderate to excellent yields ranging from 81–98% were obtained for all the combinations. The weak sensitivity to electron effects is very interesting for electron-rich substrates, which are less straight forward in transition-metal-catalyzed reactions[23, 24].

Furthermore, the catalytic system could tolerate a variety of functionalized aryl halides during the reaction, including nitrile, nitro, acetyl and ether groups (Table 2, products 4–6, 8)[21, 22]. It is noteworthy that the reaction is highly chemoselective. For example, imidazole could be selectively arylated with aryl halides bearing amino or hydroxyl group in good yields without the formation of diaryl ethers, diarylamines or other coupling side products (Table 2, products 9 and 10)[22, 25]; these functional groups require to be protected before catalysis in studies reported previously[21, 22].

We then successfully applied these reaction conditions to the reaction with a variety of imidazole derivatives and aryl bromides (Table 3). Most of the imidazole derivatives and indole exclusively afforded the corresponding products 12–20[9,12,21,28] in good to excellent yields (70–90%) under the optimized reaction conditions. The reaction was less sensitive to steric hindrance on the imidazoles as compared to Ullmann-type condensations. The sterically hindered 2-methylimidazole and 2-ethyl-4-methylimidazole could undergo selective N-arylation with 2-bromo-pyridine to give the corresponding 2-(2-methyl-1H-imidazol1-yl)pyridine (16), and 2-(2-ethyl-4- methyl-1H-imidazol-1-yl)pyridine (20) with 86% and 70% yield respectively. Characterisation data for the products are given in Table S1 (Supplementary data).

In summary, the 1,8-naphthyridine copper(I) complex (C1) which was synthesized through a non-catalyst C($sp^3$)–H methylenation, catalyzed the cross-coupling reactions of N-arylation of imidazoles with a low catalyst loading (1%, molar fraction) and cheap base even under aerobic conditions. Simple experimental procedure, easily available and synthesis catalyst, and tolerance with diverse functional groups make the present methodology attractive. Further applications of other catalysis to other reaction or biologically important molecules are still in progress.

## Supplementary data

Supplementary data associated with this article are available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJCA_57A(02)181-185_SupplData.pdf.

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