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# N-arylation of indoles with aryl halides using copper/glycerol as a mild and highly efficient recyclable catalytic system

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## ABSTRACT

A simple, efficient, and inexpensive copper catalyzed protocol has been developed for cross-coupling of indoles with aryl halides by using glycerol as a green recyclable solvent and DMSO as an additive. The reaction was carried out at low catalyst loading furnishing various *N*-aryl indoles in good to excellent yield. This copper/glycerol mixture was recycled up to four runs without any loss in its catalytic activity.

The *N*-aryl heterocycles are an important class of nitrogen containing compounds, that play a vital role in natural products, agrochemicals, material, and pharmaceutical products.[1] The *N*-aryl indoles are of much interest as antiallergic,[2] antipsychotic agents,[3] analgesic,[4] antiestrogen,[5] cyclooxygenase (COX)-1 inhibitors,[6] COX-2 inhibitors,[7] melatonin receptor MT1 agonists,[8] herbicidal agents,[9] and anti HIV-1 agents.[10] Furthermore, they are also used as important building blocks in the synthesis of various biologically active compounds.[11] Hence the development of simple and efficient methodology for the synthesis of *N*-aryl indole has attracted much attention in the past decades. Traditionally, *N*-aryl indoles have been synthesized by Ullmann-type cross coupling reactions.[12] However, this method requires high temperature and the use of stoichiometric amounts of copper catalyst thereby limiting its applications. The alternative procedure includes the palladium catalyzed coupling of heterocycles with aryl halides under mild reaction conditions.[13] However, the use of more toxic and expensive palladium catalyst limits the attractiveness of these transformations.

Subsequently, much progress has been made for *N*-arylation of indoles in Ullmann-type coupling to soften reaction conditions by employing the correct combinations of copper catalysts, ligands, bases, and other additives.[14] However, most of these protocols require ligands thereby increasing the cost. In addition toxic and non recyclable reaction media (DMF, DMSO) make protocols non greener. Recently, some researchers reported N-arylation of heterocycles in an aqueous medium because of its low cost, safety, and environmentally benign nature.[15] However, these protocols have limitations such as low solubility of substrates and ligands in aqueous medium, microwave heating and limited substrate scope. Hence, to develop an economical and sustainable protocol for this transformation that operates under environmentally favorable condition is of great interest. The progress toward more greener and recyclable reaction media such as glycerol, PEG, and ionic liquid had recently been made in cross coupling reactions.[16] Glycerol is one of the most economical and environmentally benign solvents and has triggered research in the development of new strategies for coupling reactions because of its versatile physicochemical properties such as high polarity, low flammability, high boiling point, biodegradability, and ability to dissolve both organic as well as inorganic compounds. With the increase in biodiesel manufacture world-wide, the market saturation of glycerol, a by-product of biodiesel is inevitably increasing.[17] Here, we report mild and highly efficient methodology for N-arylation of indoles with aryl halides using a copper catalyst and glycerol as a green and recyclable solvent (Scheme 1).

Initially, to optimize the reaction condition indole (**1a**) and iodobenzene (**2a**) were chosen as a model substrate for the C–N coupling reaction by using CuI catalyst in glycerol at 120 °C. Under this condition, the *N*-aryl indole (**3a**) was obtained in 47% yield (Table 1, entry1). Recent studies show that the DMSO acts as an oxidant for metal species in cross coupling reaction.[18] In order to improve the yield of *N*-aryl indole (**3a**), we performed the above reaction using 1 equiv of DMSO as additive. Interestingly *N*-aryl

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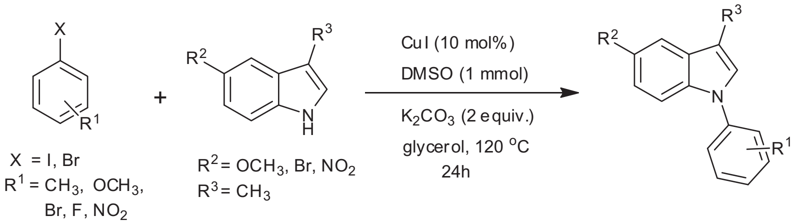
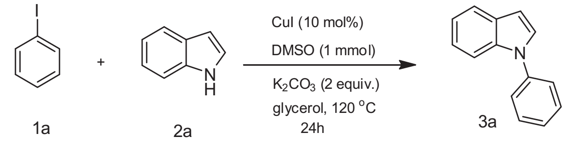


**Scheme 1.** Copper catalyzed N-arylation of indoles with aryl halides.

**Table 1**
Screening reaction conditions for N-arylation of indole with iodobenzene[a]



| Entry | Catalyst | Base | Time (h) | Temp (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | CuI | $K_2CO_3$ | 24 | 120 | 91, 47[c] |
| 2 | CuCl | $K_2CO_3$ | 24 | 120 | 79 |
| 3 | CuBr | $K_2CO_3$ | 24 | 120 | 75 |
| 4 | $CuCl_2$ | $K_2CO_3$ | 24 | 120 | 50 |
| 5 | $Cu_2O$ | $K_2CO_3$ | 24 | 120 | 70 |
| 6 | $Cu(OAc)_2{\cdot}5H_2O$ | $K_2CO_3$ | 24 | 120 | 53 |
| 7 | CuO | $K_2CO_3$ | 24 | 120 | 43 |
| 8 | $CuSO_4{\cdot}5H_2O$ | $K_2CO_3$ | 24 | 120 | 49 |
| 9 | — | $K_2CO_3$ | 24 | 120 | — |
| 10 | CuI | — | 24 | 120 | Trace |
| 11 | CuI | KOH | 24 | 120 | 74 |
| 12 | CuI | $Cs_2CO_3$ | 24 | 120 | 64 |
| 13 | CuI | $KO^tBu$ | 24 | 120 | 62 |
| 14 | CuI | $Na_3PO_4$ | 24 | 120 | 43 |
| 15 | CuI | $Et_3N$ | 24 | 120 | 49 |
| 16[d] | CuI | $K_2CO_3$ | 24 | 120 | 63 |
| 17 | CuI | $K_2CO_3$ | 24 | 110 | 72 |
| 18 | CuI | $K_2CO_3$ | 20 | 120 | 80 |

[a] Reaction conditions: iodobenzene (1 mmol), indole (1.5 mmol), Cu catalyst (0.1 mmol), base (2 mmol), DMSO (1 mmol), glycerol (2 ml), 120 °C, 24 h.
[b] GC yield.
[c] Reaction carried out without DMSO.
[d] CuI (0.05 mmol).

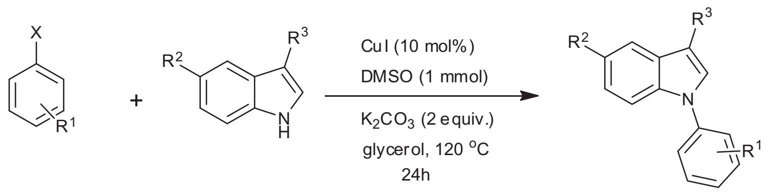
indole (**3a**) was obtained in 91% yield (Table 1, entry 1). Encouraged by this result, we screened various copper catalysts and bases for the model reaction (Table 1). It was observed that among the various screened copper catalysts, CuI gave the best yield of the desired product and hence was used for further studies (Table 1, entries 1–8), whereas no product formation was observed in the absence of copper catalyst (Table 1, entry 9). Subsequently, we screened various bases for this transformation and it was observed that the base plays an important role; in the absence of base very less product was formed (Table 1, entry 10). Among screened bases, $K_2CO_3$ exhibited higher activity (Table 1, entries 1 and 11–15). We have also screened various solvents such as DMSO, DMF, toluene, and water for this transformation. It was found that DMSO and DMF provided trace amount of the desired product and solvents like toluene and water were ineffective for N-arylation of indole. However, decreasing the catalyst loading from 10 mol % to 5 mol %, decreases yield of **3a** (Table 1, entry 16). In addition, the effect of reaction temperature and time was also investigated. It was observed that the yield of **3a** decreases with a decrease in temperature (Table 1, entry 17). While decreasing the time from 24 h to 20 h, low yield of **3a** was observed indicating that 24 h was an optimum time required for completion of the reaction (Table 1, entry 18).

With these optimized reaction conditions in hand, we have studied the scope and limitation of developed protocol for N-arylation of various heterocycles. As illustrated in Table 2, the reaction of *N*-heterocycles with various halides proceeds efficiently to furnish a wide range of *N*-aryl heterocycles in good to excellent yield.[20] Firstly, we have screened various indole derivatives and it was observed that 3-methyl-1*H*-indole gave excellent yield of 3-methyl-1-phenyl-1*H*-indole (Table 2, entry 2), whereas 5-methoxy-, 5-bromo-1*H*-indole on coupling with iodobenzene afforded good yield of corresponding products (Table 2, entries 3 and 4). The prominent feature of developed protocol is that the bromo substituent at C-5 position of indole remained intact.

The indole with electron withdrawing substituent such as 5-nitro-1*H*-indole also provided acceptable yield (65%) of 5-nitro-1-phenyl-1*H*-indole (Table 2, entry 5). Interestingly, less reactive aryl halide such as bromobenzene also couples with indole derivatives furnishing *N*-aryl indoles in good to appreciable yields (Table 2, entries 6 and 7). The reaction of indole with 1-bromo-2-iodobenzene afforded the selective mono coupling 1-(2-bromophenyl)-1*H*-indole in good yield under optimized reaction condition (Table 2, entry 8). Next, electronically different halo derivatives with indole were also studied. The *ortho*-substituted 1-iodo-2-methoxybenzene afforded the 1-(2-methoxyphenyl)-1*H*-indole in 73% yield indicating no steric effect in the coupling reaction (Table 2, entry 9). Furthermore, good to excellent yields were achieved regardless of the electronic nature of the substituents on the aryl iodide, and no considerable electronic effects were observed for both *meta*- and *para*-substituted aryl iodides (Table 2, entries 10–12). We extended the substrate scope of the present protocol by replacing the indoles with other heterocycles. The treatment of pyrrole with aryl iodide afforded the corresponding 1-phenyl-1*H*-pyrrole in 52% yield (Table 2, entry 13). Further, various imidazole and pyrazole derivatives such as 1*H*-imidazole, 2-phenyl-1*H*-imidazole, and 3-phenyl-1*H*-pyrazole were coupled with aryl iodide furnishing the corresponding **3l**, **3m**, and **3n** in 67%, 64%, and 62% yields respectively (Table 2, entries 14–16).

In consideration of economical view of the developed methodology, reusability of the catalytic system was examined for N-arylation of (**2a**) with (**1a**) as model reaction after the extraction of product with diethyl ether. 1 mmol of fresh DMSO should have been complemented to the reaction system before the next run, as very less product was observed for next run without fresh addition of DMSO. The recovered glycerol layer containing copper catalyst accomplishes the respective transformation up to four times with iodobenzene and indole as a substrate (Table 3). In this

**Table 2**
N-Arylation of NH-heterocycles with various aryl halides [a]



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| Entry | Aryl halide | NH-heterocycles | Product | Yield[b] (%) |
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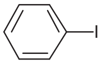
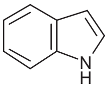
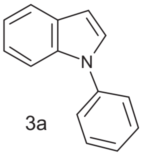
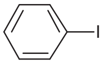
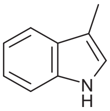
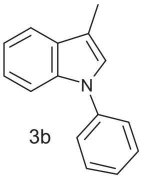
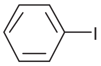
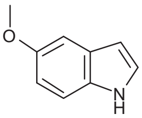
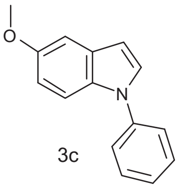
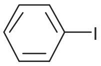
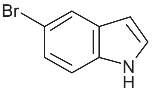
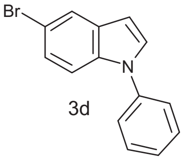
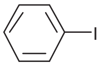
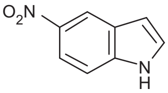
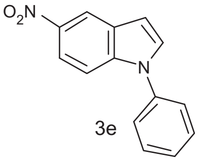
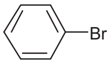
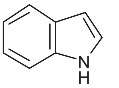
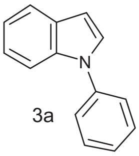
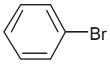
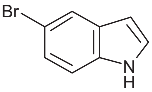
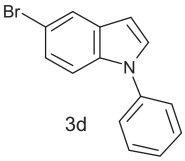
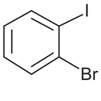
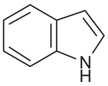
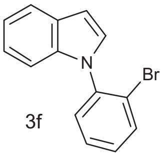
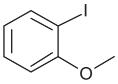
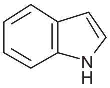
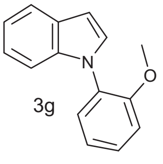
| 1 |  |  |  3a | 88 |
| 2 |  |  |  3b | 92 |
| 3 |  |  |  3c | 80 |
| 4 |  |  |  3d | 78 |
| 5 |  |  |  3e | 65 |
| 6 |  |  |  3a | 78 |
| 7 |  |  |  3d | 71 |
| 8 |  |  |  3f | 76 |
| 9 |  |  |  3g | 73 |

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**Table 2** (*continued*)

| Entry | Aryl halide | NH-heterocycles | Product | Yield[b] (%) |
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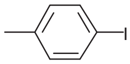
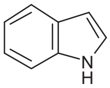
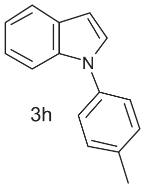
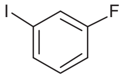
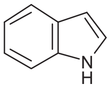
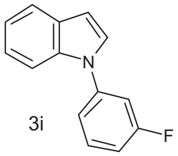
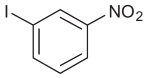
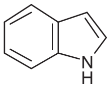
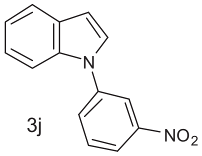
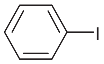
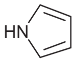
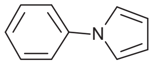
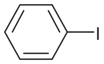
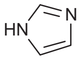
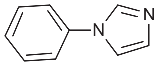
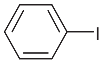
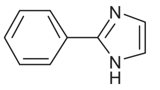
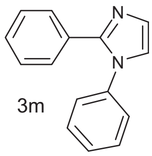
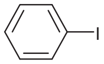
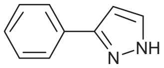
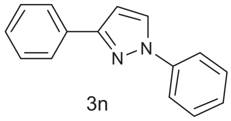
| 10 |  |  |  3h | 85 |
| 11 |  |  |  3i | 88 |
| 12 |  |  |  3j | 73 |
| 13 |  |  |  3k | 52 |
| 14 |  |  |  3l | 67 |
| 15 |  |  |  3m | 64 |
| 16 |  |  |  3n | 62 |

[a] Reaction conditions: aryl halides (1 mmol), NH-heterocycles (1.5 mmol), $K_2CO_3$ (2 mmol), CuI (0.1 mmol), DMSO (1 mmol), glycerol (2 ml), 120 °C, 24 h.

[b] Isolated yield.

**Table 3**
Recyclability study of catalyst for N-arylation of indole with iodobenzene[a]

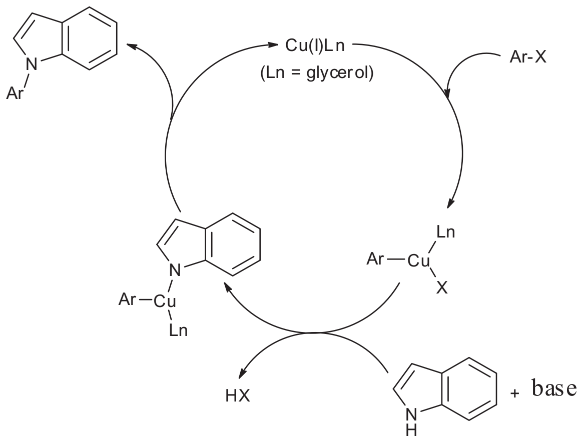
| Run | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Yield[b] | 91 | 89 | 88 | 86 |

[a] Reaction conditions: iodobenzene (1 mmol), indole (1.5 mmol), $K_2CO_3$ (2 mmol), CuI (0.1 mmol), DMSO (1 mmol), glycerol (2 ml), 120 °C for 24 h.

[b] GC yield.

context, we performed the ICP-AES analysis of fourth recycle run and observed only 0.056 ppm of copper in solution which revealed no significant leaching of copper. Thus, the developed protocol shows an efficient recycling of both metal and reaction media with respect to the heterogeneous catalytic system where only metal complex has been recycled and reused.

Based on our observation and literature studies, we assume that additive DMSO[18] helps in an oxidative addition of aryl halide with metal and glycerol[19] acting as a ligand that might be coordinating with metal and helps in accelerating reaction toward the product. Further investigation on the role of DMSO as an additive and glycerol as a ligand in the reaction mechanism is under progress (See Scheme 2).



**Scheme 2.** Plausible mechanism for the N-arylation.

In conclusion, we have established an efficient Cu(I)iodide catalyzed N-arylation of indole with a variety of aryl halides by using glycerol as a green, environmentally benign, safe, and non toxic reaction media. The homogeneous system containing copper catalyst, base, and glycerol could be reused for four runs after simple extraction of the product with diethyl ether. Thus, the developed protocol sounds to be highly efficient, greener, economically and environmentally more acceptable.

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20. General experimental procedure: To a 25 ml two-necked round-bottom flask was placed a mixture of aryl iodide (1 mmol), indole (1.5 mmol), CuI (0.1 mmol), $K_2CO_3$ (2 mmol), and DMSO (1 mmol) in 2 ml glycerol. The reaction mixture was heated in an oil bath at 120 °C for 24 h with continuous stirring. After completion of reaction monitored by TLC, the reaction mixture was cooled to room temperature and was extracted with diethyl ether three times (3 × 10 ml). The combined organic layers were washed with brine solution and dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (60–120 mesh) to provide the *N*-aryl indole in 88% yield. The remaining glycerol/copper catalytic mixture was reused for further recycling study by adding fresh DMSO (1 mmol) to the catalytic system. All the products are well known in the literature and were confirmed by comparison of their spectroscopic data with literature data.