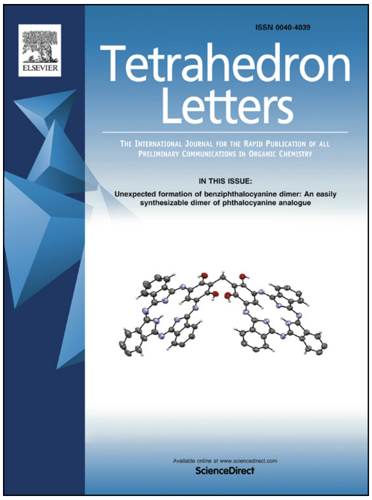

Copper^{II} phthalocyanine as an efficient and reusable catalyst for the N-arylation of nitrogen containing heterocycles

Kumar Karitkey Yadav, Uma Narang, Soumee Bhattacharya, Shive M.S. Chauhan

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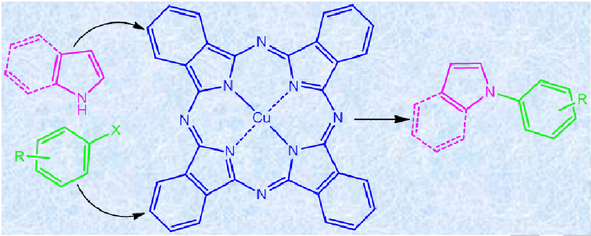

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Copper^{II} phthalocyanine as an efficient and reusable catalyst for the N-arylation of nitrogen containing heterocycles

Kumar Karitkey Yadav,[a] Uma Narang,[a] Soumee Bhattacharya[a] and Shive M.S. Chauhan[a]*

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ABSTRACT

Copper phthalocyanine (Cu^{II}Pc) was found to be an efficient catalyst for the catalyzed N-arylation of N-H heterocycles with aryl iodides and bromides under mild reaction conditions. A variety of hindered and functionalized N-H heterocycles and aryl halides were successfully used as the substrates for the given catalytic reaction and were transformed in good to excellent yields.

N-Arylazoles are important building blocks in pharmaceutical,[1] agrochemical,[2] material sciences[3] and in organic synthesis.[4] Nitrogen containing heterocycles are of interest as antipsychotic,[5] antiallergic,[6] COX-2 inhibitors,[7] herbicidal agents,[8] and melatonin receptor MT1 agonists.[9] These heterocycles are also used as biological intermediates in the synthesis of many biologically active compounds.[10] The copper-catalyzed Ullmann-Goldberg coupling[11] is a traditional method for the synthesis of N-arylated heterocycles with the reaction of aromatic halides. However, the harsh reaction conditions such as the necessity of a stoichiometric amount of copper catalyst,[12-14] high reaction temperatures (125-250°C),[15] and the low to moderate yields of the products[15] have undoubtedly prevented these reactions from being employed to their full potential.

Recently different Pd based catalytic systems along with different sterically hindered phosphine ligands have been developed for the cross coupling of N-H heterocycles and aryl halides.[16] After the discovery of Ullmann type coupling reaction of copper catalyzed N-arylation of heterocycles in the presence of ligands, the economic significance of copper led to a renaissance of interest. The efficient ligands which were utilized along with copper salts, were from the groups of amino acids,[12] diimines,[13] diamines, phosphines ligands,[14] pyridine functionalized 1,3-diketones,[17] natural alkaloids,[18] 4,7-dimethoxy-1,10-phenanthroline,[19] diazabutadiene,[20] benzotriazole,[21] etc. In recent years several other transition metals based catalytic systems such as Fe,[22] Fe/Cu,[23] Ni,[24] Ru[25] and Cd[26] in combination with various ligands has been reported for C-N coupling reactions. Unsatisfactory product yields, long reaction times, higher temperature and use of relatively expensive reagents are the drawbacks associated with these methods. Particularly, some of the ligands applied in these reported reactions are not commercially available and are difficult to synthesize in lab. Hence, the development of an efficient, mild and versatile method for the C-N coupling reaction of N-H heterocycles and aryl halides for the synthesis of N-aryl heterocycles is an active ongoing research area and there is scope for further improvement toward milder reaction conditions and avoid of expensive ligands.

Phthalocyanine metal complexes (MPcs) are purely synthetic molecules and are structurally analogous to porphyrin complexes.[27] Due to the structural similarity with porphyrin metal complexes, it shows bioinspired chemistry associated with porphyrin complexes.[28] Recently phthalocyanines have been successfully utilized as catalysts for different synthetic reactions.[29-32] The catalytic properties of metallophthalocyanines depend on the metal atom and structure of the phthalocyanine moiety. Different metals are inserted in the core of the phthalocyanine ring to utilize them in specific reactions.

In connection with our ongoing research for the development of simple, economic and efficient methods for metallophthalocyanine catalyzed organic reactions,[29, 31-32] herein we report the first example the N-arylation of N-H heterocycles with aryl halides directly catalyzed by copper^{II} phthalocyanines without any ligands under mild reaction conditions in DMSO with satisfactory results. The current catalytic system possess several advantages over reported procedures as no additional ligand is used, low reaction temperature, low catalyst loading, substrate selectivity, simple work up procedure with excellent yields and reusability of the catalyst.

The metallophthalocyanines were synthesized by the tetramerization of phthalonitriles and metal salts by following the procedure reported by us.[33] Metallophthalocyanine was purified, characterized and used as the catalysts for the N-arylation reactions of N-H heterocycles and aryl halides in the presence of base.

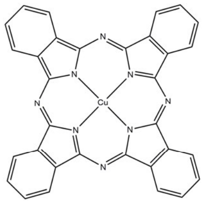
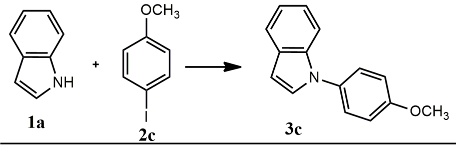


Figure 1. Structure of the Copper^{II} phthalocyanine (**4**).

Table 1. Screening of the catalytic system for the reaction of indole and 4-methoxyiodobenzene



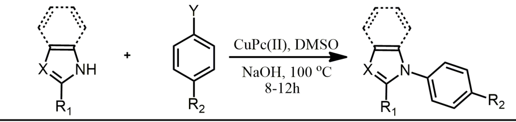
1a **2c** **3c**

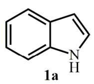
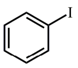
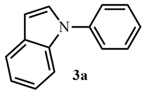
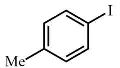
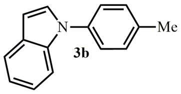
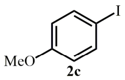
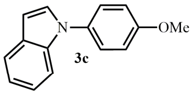
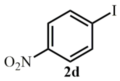
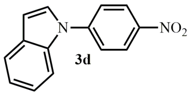
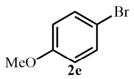
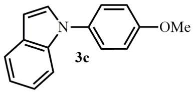
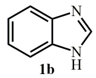
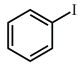
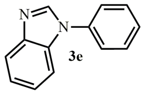
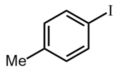
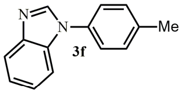
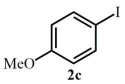
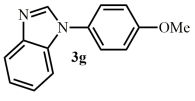
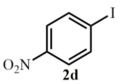
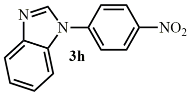
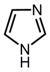
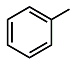
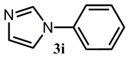
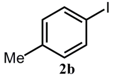
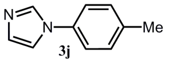
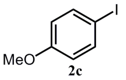
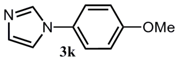
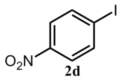
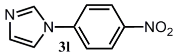
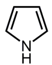
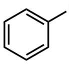
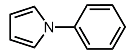
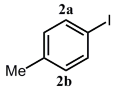
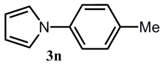
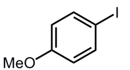
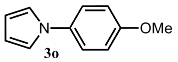
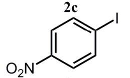
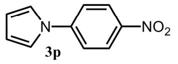
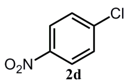
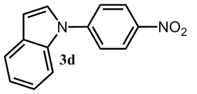
Entry	Catalyst^a	Solvent	Base	Temp	Yield^b
1	-	DMSO	NaOH	120°C	0
2	Zn(II)Pc	DMSO	NaOH	120°C	5
3	Co(II)Pc	DMSO	NaOH	120°C	8
4	Ni(II)Pc	DMSO	NaOH	120°C	12
5	Cu(II)Pc	DMSO	NaOH	120°C	99
6	Cu(II)Pc	DMF	NaOH	120°C	92
7	Cu(II)Pc	EtOH	NaOH	120°C	60
8	Cu(II)Pc	Toluene	NaOH	120°C	24
9	Cu(II)Pc	H_2O	NaOH	120°C	0
10	Cu(II)Pc	DMSO	NaOEt	120°C	70
11	Cu(II)Pc	DMSO	K_2CO_3	120°C	0
12	Cu(II)Pc	DMSO	NaOH	100°C	99
13	Cu(II)Pc	DMSO	NaOH	80°C	86
14	Cu(II)Pc^c	DMSO	NaOH	100°C	72

[a] 1 mol% of the catalyst was used, reaction was carried out for 12 h; [b] isolated yield; [c] 0.5 mol% catalyst was used.

To optimize the catalytic reaction conditions, indole (**1a**) and 4-methoxyiodobenzene (**2c**) was selected as the model substrate. The catalytic activity of metallophthalocyanines for the N-arylation of indole (1 mmol) with 4-methoxyiodobenzene (1 mmol) was evaluated in the presence of NaOH at 120°C for 12h in DMSO and results are presented in table 1. In the absence of catalyst, the reaction did not proceed and the starting materials were recovered as such from the reaction (Table 1, entry1). When Cu^{II}Pc (0.01 mmol) was used as catalyst, indole reacted with 4-methoxyiodobenzene to give the 1-(4-methoxyphenyl)-1*H*-indole (**3c**) as a product. When Cu^{II}Pc was replaced with Zn^{II}Pc, Ni^{II}Pc and Co^{II}Pc and used as catalysts for the current reaction, products were obtained in low yields (Table 1, entry 2-5). When solvent was changed from DMSO to DMF, ethanol, toluene and water, product yield was constantly decreased and in water reactant and catalyst were recovered as such from the reaction medium. Thus DMSO was observed as the best solvent for the current reaction. Further the effect of change of base was screened and NaOEt, K_2CO_3 and NaOH were used as the base for the current catalytic reaction; out of which NaOH gave the best results. The decrease of temperature from 120°C to 100°C did not affect the yield of the reaction but further decrease to 80°C lowered the yield of the reaction (Table 1, entry 12-13). On decreasing the amount of catalyst from 1 mol% to 0.5 mol%, yield of product was decreased.

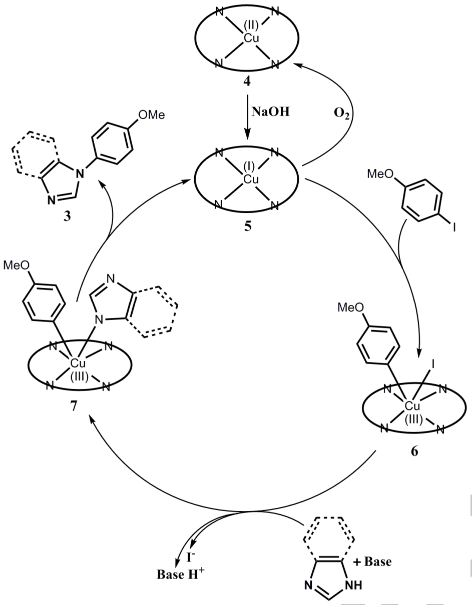
Table 2. Reaction of N-H heterocycles with aryl halides catalyzed by Cu^{II}Pc and NaOH in DMSO



Entry	N-H Hterocycle^a	Aryl halide	Product	Yield^b	Ref
1	 1a	 2a	 3a	99%	33
2	1a	 2b	 3b	98%	33
3	1a	 2c	 3c	96%	33
4	1a	 2d	 3d	100%	33
5	1a	 2e	 3c	94%	33
6	 1b	 2a	 3e	98%	34
7	1b	 2b	 3f	97%	34
8	1b	 2c	 3g	97%	34
9	1b	 2d	 3h	99%	35
10	 1c	 2a	 3i	98%	34
11	1c	 2b	 3j	98%	34
12	1c	 2c	 3k	96%	34
13	1c	 2d	 3l	100%	34
14	 1d	 2a	 3m	97%	36
15	1d	 2b	 3n	97%	36
16	1d	 2c	 3o	95%	36
17	1d	 2d	 3p	98%	36
18	1a	 2d	 3d	73%	33

[a] Reaction condition: 1 mol% catalyst, 1 mmol N-H heterocycle, 1 mmol aryl halide at 100°C for 8-12h; [b] Isolated Yield.

After getting a good catalytic system, the reaction was further explored for different N-H heterocycles and different electron rich and electron deficient aryl halides (Table 2). In general, most of the substituted aryl iodides and electron-deficient aryl bromides afford the *N*-arylheterocycles in good to excellent yields[34]. Unfortunately the aryl chlorides react slower than aryl bromides and aryl halides and give moderate yield of product. Aryl halides with electron withdrawing substituent give better yield than aryl halides with electron donating substituents. Substituted benzimidazole undergoes arylation reactions and gave better yield of products. The reaction proceeds with different types of azoles such as imidazole, pyrrole, benzimidazole and indole; and in all cases good yields of arylated product were obtained. Thus the current catalytic system is suitable for different types of Carbon-Nitrogen bond forming reactions.



Scheme 1: Proposed reaction pathway for the current catalytic cycle.

The interaction of aryl halide with $Cu^{II}Pc$ was studied by UV-Visible spectroscopy in DMSO, but no significant changes were observed. The current catalytic system possesses several advantages over other catalytic systems such as; the lower reaction temperature with lesser reaction time, reaction proceeds without an inert atmosphere, catalytic system requires low catalyst loading (1 mol%), simple work up procedure with efficient yield of products, and catalyst is recoverable and can be reused without much loss of its catalytic activity.

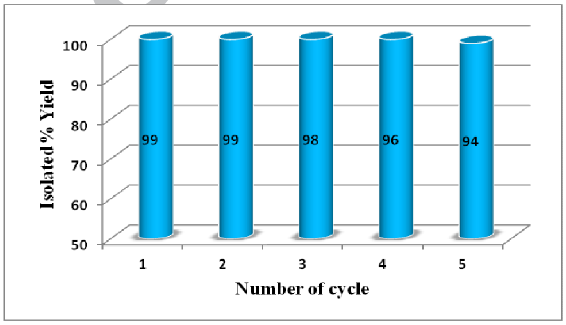


Figure 2. Reusability of the copper phthalocyanine (**4**).

After getting the successful results for different heterocycles with different substituted aryl halides, the recyclability of the catalyst was examined. The stability of the catalyst was checked with UV-Visible spectroscopy and the catalyst was found to be stable in the current catalytic system. The presence of an unchanged UV-Vis spectrum of the catalyst **4** after the reaction (after 5th runs) further confirmed its stability in the current catalytic system. The $Cu^{II}Pc$ catalyst was reused up to five catalytic cycles during the reaction of benzimidazole and 4-methoxtbromobenzene. The catalytic activity remains constant. The yield of the product by the isolated reused catalyst is shown in figure 2. Thus the catalyst can be easily separated from the reaction mixture and can be reused up to five catalytic cycles without any loss of its catalytic activity.

Based on the previous literature reports,[35-37] a suitable reaction mechanism for the current catalytic reaction is proposed (Scheme 1). $Cu^{II}Pc$ get reduced to $Cu^{I}Pc$ (**5**) by NaOH under nitrogen in DMSO. The reduced $Cu^{I}Pc$ may revert back to $Cu^{II}Pc$ (**4**) by the action of O_2. This $Cu^{I}Pc$ undergoes oxidative addition with aryl halide and is oxidized to $Cu^{III}Pc$ (**6**).[37-38] The species **6** undergoes base catalyzed group transfer reaction with N-H heterocycle to generate intermediate **7**.[37-38] The species **7** undergoes reductive elimination to give the product (**3**) and $Cu^{I}Pc$ (**5**).[37-38] Thus the regenerated $Cu^{I}Pc$ (**5**) again restart the cycle. After the completion of the reaction, the $Cu^{I}Pc$ get oxidized back to $Cu^{II}Pc$ by action of O_2 or water.

In conclusion, we have reported that Copper phthalocyanine ($Cu^{II}Pc$) is an excellent, inexpensive, reusable and simple catalyst for the N-arylation of N-H heterocycles with a diverse range of aryl halides providing excellent yields of products. The current catalytic system offers various advantages over other literature methods such as high selectivity, higher yield of product, shorter reaction time, lower reaction temperature, simple work-up procedure and reusability of the catalyst.

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34. General catalytic procedure: In a 50 mL RB, N-H heterocycles (1.0 mmol), aryl halide (1 mmol), Cu(II)Pc (0.01 mmol), NaOH (1.5 mmol) and DMSO (2 mL) was added. This reaction mixture was stirred to a preheated oil bath at 100^{o}C for 8-12 h. After completion of the reaction, it was cooled to room temperature and 20 mL ethyl acetate was added. It was filtered; solid catalyst was separated and washed with 2x5 mL ethyl acetate. The washing and filtrate were combined and washed with water. Ethyl acetate was removed under reduced pressure and product was purified with column chromatography.
    1-Phenyl-1*H*-indole (3a): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.78 (m, 1H), 7.24-7.21 (m, 1H), 7.36-7.32 (m, 2H), 7.18 (d, 4H), 7.14-7.12 (m, 2H), 6.66-6.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.82, 135.82, 129.63, 1129.30, 127.95, 126.47, 124.37, 122.38, 121.13, 120.34, 110.52, 103.58; MS (EI, m/z): 193 $[M]^+$.
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- ✓ Copper phthalocyanine is used for the N-Arylation of different N-H heterocycles.
- ✓ Reaction does not require any additional ligand.
- ✓ Reaction is carried out at low reaction temperature.
- ✓ Different aryl halides were successfully utilized.
- ✓ Catalyst is easily separated and reused up to five catalytic cyles.