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Glycerol ingrained copper: an efficient recyclable catalyst for the N-arylation of amines with aryl halides

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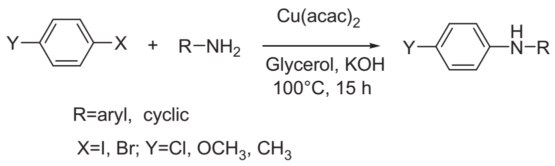
ABSTRACT

A copper-catalyzed coupling reaction of aryl halides with various aromatic and cyclic amines by using glycerol as a green recyclable solvent has been developed efficiently. The glycerol embedded copper catalyst could readily be separated from the reaction mixture and reused for several runs without any loss in catalytic efficiency.

In recent years, development of recyclable catalytic system using green solvents obtained from renewable resources has attracted much interest.[1] With the increase in biodiesel production world-wide, the amount of glycerol, a by-product of biodiesel production is inevitably increasing. The recent studies have established that glycerol owing to its desirable physicochemical properties such as high polarity, low toxicity and flammability, high boiling point and ability to dissolve both organic and inorganic compounds can be considered as a green solvent for various organic transformations.[2–9] N-Arylation of amines is an important reaction because arylamines are ubiquitous in the tremendous important fields such as pharmaceuticals, agrochemicals, pigments, and electronic materials.[10–14] The classical Ullmann reaction has been known for N-arylation in the presence of copper at higher temperature.[15] However, the utility of classical Ullmann coupling is mainly limited by its harsh reaction conditions, such as high temperatures (ca. 200 °C), the stoichiometric use of copper compounds, and poor substrate scope.[16] Subsequently, various reports have appeared for N-arylation of amines using copper ligand or/and copper salts as catalysts.[17,18] Very recently, ligand-free N-arylation of amines by using CuI salts has appeared, which seems to be a promising approach for the synthesis of N-arylamines.[19] However, in most of the cases reported methods require toxic and volatile higher boiling solvents like (DMF, DMSO) to perform the reaction.[20] Taking into account the impact of chemical processes on the environment, the search for innovative concepts for the substitution of volatile organic solvents has become a subject of intensive research in recent decades. Recently, more environmentally friendly and recyclable solvents such as low molecular-mass PEG and ionic liquids were evaluated as reaction media in cross coupling reactions.[19b,21] These solvents allow easy separation of products as well as catalyst recycling. However, high prices and lack of data about the toxicity and bio-compatibility for ionic liquids are still debatable. In continuation of our on-going research on the development of enviro-economic synthetic methodologies,[22] herein we report an efficient methodology for the N-arylation of various amines including aromatic and cyclic amines by using glycerol as green solvent and copper acetylacetonate as catalyst (Scheme 1). In the present work copper embedded glycerol could efficiently be reused for several runs.

For initial studies we have chosen N-arylation of aniline with iodobenzene as the model reaction. The results of these optimization experiments are summarized in Table 1. At first, we studied the effect of catalyst concentration on the reaction by changing the amount of the copper acetylacetonate catalyst from 1 to 5 mol % as shown in Table 1 (entries 1–3). The N-arylation of iodobenzene (1.0 mmol) and aniline (1.5 mmol) with $Cu(acac)_2$



Scheme 1. Copper-catalyzed *N*-arylation of amines.

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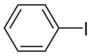
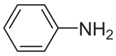
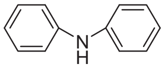
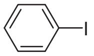
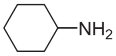
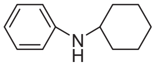
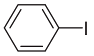
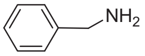
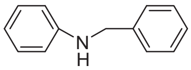
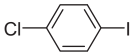
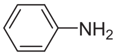
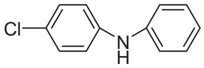
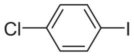
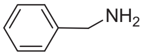
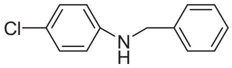
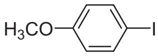
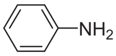
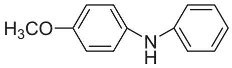
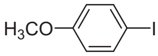
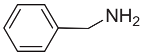
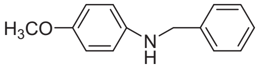
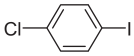
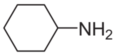
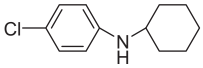
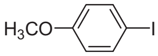
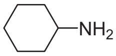
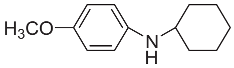
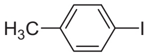
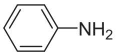
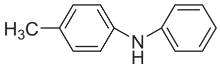
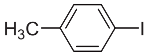
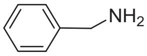
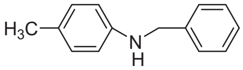
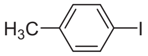
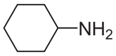
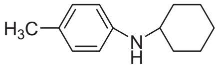
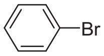
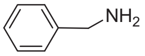
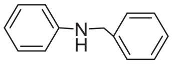
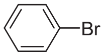
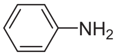
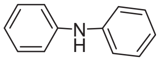
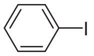
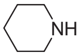
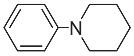
Table 1
Screening reaction conditions for *N*-arylation of aniline with iodobenzene[a]

Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Base	Conv[b] (%)
1	$Cu(acac)_2$(1)	80 100 100	12 15 15	KOH	60 90[c] 95[d]
2	$Cu(acac)_2$(2)	100	15	KOH	100
3	$Cu(acac)_2$(5)	100	12	KOH	96
4	$Cu(acac)_2$(1)	100	15	--	--
5	–	100	15	KOH	30
6	$Cu(acac)_2$(1)	100	15	K_2CO_3	94
7	$Cu(acac)_2$(1)	100	15	KO^tBu	97
8	$Cu(OAc)_2$(1)	100	15	KOH	85
9	$CuCl_2$(1)	100	15	KOH	82
10	CuI(1)	100	15	KOH	87
11	$Cu(acac)_2$(1)	100	15	KOH	60[e]
12	$Cu(acac)_2$(1)	100	15	KOH	42[f]

[a] Reaction conditions: aniline (1.5 mmol), iodobenzene (1.0 mmol).
[b] Conversion determined by GC–MS.
[c] The reaction was carried out at 80 °C for 12 h and then increased the temperature to 100 °C for additional 3 h.
[d] Reaction was performed at 100 °C for 15 h.
[e] Reaction was performed in DMSO.
[f] Reaction was performed in DMF solvent in place of glycerol.

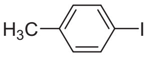
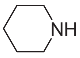
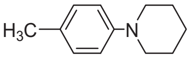
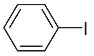
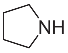
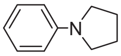
(1 mol %) in glycerol (5.0 mL) in the presence of KOH (2 mmol) at 80 °C, afforded biphenylamine in 58% isolated yield in 12 h (Table 1, entry 1). However, by increasing the reaction time from 12 to 15 h and temperature to 100 °C, the product yield was found to be increased (Table 1, entry 1). Furthermore, by increasing the catalyst concentration from 1 to 2 mol %, the reaction was found to be increased and was completed in 15 h (Table 1, entry 2). Further, with the increase in catalyst concentration to 5 mol %, no marginal effect on the reaction rate was observed (Table 1, entry 3). Thus, based on these findings, it was concluded that the best results were obtained when the reaction temperature of the system was kept at 100 °C and reaction time was 15 h. Further, it was also observed via NMR, TLC, and column chromatography that no side products, such as Ar–Ar coupling products, were formed during the reaction. The presence of base was found to be vital and in its absence no reaction could take place under otherwise similar reaction conditions (Table 1, entry 4). Similarly, the reaction was found to be slow in the presence of KOH without adding copper catalyst under similar reaction conditions (Table 1, entry 5). Changing the base from KOH to K_2CO_3 and KO^tBu showed only a marginal change in product yield (Table 1, entries 6 and 7). Furthermore we studied the

Table 2
Copper in glycerol-catalyzed N-arylation of amines[a]

Entry	Aryl halide	Amine	Product	Yield[b] (%)
1				92
2				98
3				85
4				97
5				70
6				84
7				80
8				98
9				92
10				96
11				95
12				94
13				82
14				80
15				85

(*continued on next page*)

Table 2 (*continued*)

Entry	Aryl halide	Amine	Product	Yield[b] (%)
16				88
17				87

[a] Reaction conditions: aryl halide (1 mmol), amine (1.5 mmol), KOH (2 mmol), Cu(acac)$_2$ (2 mol %), glycerol (5 ml).

[b] Isolated yields.

coupling of iodobenzene with aniline by using different copper salts such as CuI, $CuCl_2$ and $Cu(OAc)_2$. Among various copper salts, copper acetylacetonate was found to be promising for this transformation. The results of these experiments are shown in Table 1 (entries 8–10). We also performed the reaction of aniline with iodobenzene in solvents such as DMF and DMSO under otherwise identical experimental conditions. The reaction was found to be slow and gave low yield of N-arylated product as shown in Table 1, entries 11 and 12. Thus, based on these results, the optimum reaction conditions for this transformation were found to be as follows: catalyst (2 mol %) in the presence of KOH at 100 °C and reaction time 15 h. Next, we generalized the reaction by selecting a variety of amines including aromatic, aliphatic, and cyclic under the described experimental conditions. The results are summarized in Table 2. Different primary amines including aromatic, and cyclic were coupled successfully and afforded excellent yield of the mono N-arylated product (Table 2, entries 1–14). Experiments on substituted aryl halides were carried out with OMe-, Cl, and Me-containing substrates. In all cases, the reaction progressed efficiently with >85% conversion of the substrates. The presence of Cl-substituent did not affect the reaction and corresponding 4-chloro substituted diphenylamine was obtained in 97% yield from the reaction of aniline and 4-chloro iodobenzene (Table 2, entry 4). In the present method, we could successfully use 1-bromobenzene in place of iodobenzene for the C–N coupling reaction with amines as shown in Table 2 (entries 13 and 14). Similarly, good to high yields were obtained for the cyclic secondary amines (Table 2, entries 15–17). In all cases, the reaction was found to be selective for mono N-arylation and afforded corresponding mono N-arylated products without any evidence for the formation of any by-product.

At the end of the reaction, the product was isolated by extraction with diethyl ether and the remaining glycerol layer containing copper catalyst was reused as such for the subsequent experiments. The recovered glycerol containing copper catalyst was successfully reused for six runs without any loss of catalytic activity. The results of recyclability are presented in Table 3. These results confirm that the catalytic system presented herein satisfies the conditions for heterogeneous catalysts of ease of separation, recyclability and consistent catalytic activity. The developed method shows an efficient recycling of the catalyst by using a sustainable solvent and provided higher product yields under comparatively mild reaction conditions.

Although the exact mechanism of the reaction is not known at this stage, based on the literature studies,[23] we assume that the glycerol acts as a ligand which might be coordinating with metal and playing an important role in accelerating the reaction.[24,25] Studies toward the mechanism insight and the role of glycerol in this reaction are under progress.

Table 3
Results of recycling experiments[a]

Run	1	2	3	4	5	6
Conv.[b]	94	94	92	92	90	90

[a] Conditions: iodobenzene (1 mmol), aniline (1.5 mmol), KOH (2 mmol), Cu(acac)$_2$ (2 mol %), glycerol (5 ml) at 100 °C.

[b] Conversion was determined by GC–MS.

In summary, we have developed an efficient and recyclable catalytic system by employing glycerol as a sustainable solvent for the N-arylation of various amines with aryl halides in excellent yields. Both the copper acetylacetonate and KOH base are soluble in glycerol; therefore after isolating the product by extraction with diethyl ether, catalyst and base embedded in glycerol can be successfully reused as such for several runs. The use of glycerol not only makes the product recovery easier but also provides a unique approach for the recycling of the catalyst and base. Furthermore, glycerol is greener and safer than DMF and DMSO, which makes the developed method more environmentally friendly.

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23. *General procedure for the synthesis of secondary amines:* To a 25 ml round bottomed flask containing glycerol (5 ml) were added aryl halide (1 mmol), amine (1.5 mmol), $Cu(acac)_2$ (2 mol %), and KOH (2 mmol). The resulting mixture was heated at 100 °C for 15 h under N_2 atmosphere. After completion, the reaction mixture was cooled to room temperature and was extracted with diethylether to isolate the reaction products. The combined organic layers were washed twice with brine solution (10 ml ×2) and dried over anhydrous sodium sulfate followed by the evaporation of solvent under reduced pressure to yield the crude product. The remaining glycerol layer containing copper catalyst was reused for recycling experiments. The crude product was purified by column chromatography over silica gel using ethyl acetate and hexane (2:8) as eluents; conversion and selectivity of the product was determined by GC–MS results.
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