N-Arylation Of Amines Catalyzed By Starch Supported Cu Catalyst Under Ligand-Free Conditions

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Abstract : A highly efficient and ligand-free approach for N-arylation of amines has been developed using starch supported copper catalyst under very mild reaction conditions. This protocol could not only tolerate an array of functional groups, but also achieve high chemoselectivity under the reaction conditions. The catalyst can be easily recovered and reused upto several runs without loss of significant activity.

***Keywords* - N-arylation of amines, Recyclability, Selectivity, Starch-functionalized copper(II) acetate [Star-Cu(OAc)$_2$].**

INTRODUCTION

Amines and their derivatives are the most common structural features of various naturally occuring biologically active compounds, and are widely used as basic intermediates for the preparation of dyes, solvents, fine chemicals, fluorescence probes, pharamaceuticals, agrochemicals and catalysts for polymerization [1-8]. C-N bond-formation reactions between aryl halides and amines are well known, including the SNAr reactions [9], classical Ullmann-type coupling reactions [10–12], and Buchwald-Hartwig reactions [13–15]. Amongst various C-N bond forming reactions, Pd-catalyzed C-N coupling reaction has been found to be very useful method to build aromatic amines or arylazoles [16–19]. However, considering to the cost and toxicity of both palladium catalyst and auxiliary phosphine ligands, the arylation of amines with aryl halides to form new C-N bonds still remains a field of interest. In recent years, Cu-catalyzed Ullmann-type couplings[20] have attracted more and more attention due to its easy availability and low toxicity. More recently, copper promoted N-arylation with aryl boronic acids for diverse N-H containing substrates was discovered by Chan [21-22] and Lam [23]. This methodology was further extended to include aryl stannanes [24] with limited success. However these reactions are generally slow(18 hr-13 days to proceed to completion) and carried out with either Et_3N or pyridine as base in dichloromethane. In all cases, the use of excess of aryl boronic acids is also a major limitation of the methods.

Although various methods are available for N-arylation of amines [25-28], but most of them use harsh reaction conditions and some of them use excess of reagents, making them undesirable from an environmental point of view and from an economic standpoint in case of costly or commercially unavailable reagents. So there is a scope for further innovation towards the development of protocols which work under mild conditions and give better yields.

Herein, an efficient and cost-effective procedure has been reported for the chemoselective *N*-arylation of amines using Star-Cu(OAc)$_2$ as recyclable heterogeneous catalyst under mild reaction conditions

EXPERIMENTAL

Materials

The chemicals used were purchased from Aldrich chemical company and Merck. The products were characterized by their spectral data and comparison of their physical data with those of known samples. The ^{1}H NMR data were recorded in $CDCl_3$ or $CDCl_3$+DMSO-d_6 on Bruker DPX 200 (200 MHz) spectrometer using TMS as an internal standard. The IR spectra were recorded using KBr disc on Perkin-Elmer FTIR spectrophotometer. Mass spectral data were recorded on Esquire 3000 (ESI). Thermal analysis was carried out on DTG-60 Shimadzu make thermal analyzer with heating rate of 10 C/min. X-ray diffraction patterns were measured on a Bruker AXSD8 X-ray diffraction spectrometer. SEM was recorded using Jeol make T-300 Scanning Electron Microscope and Transmission Electron Microscope (TEM) on H7500 Hitachi. The amount of copper in Star-Cu(OAc)$_2$ was determined on double beam Atomic Absorption Spectrophotometer (AAS), GBC 932 AB manufactured in Australia. The catalyst was stirred in dil. HCl for 10 h and then subjected to AAS analysis.

General procedure for the preparation of starch-functionalized Cu(OAc)$_2$

Preparation of 3-aminopropyl starch (APS)

Corn starch (15 g) was taken in a round bottom flask (500 mL) containing double distilled water (300 mL) and stirred at 110 ºC for 24 h. After this time, the vessel was cooled to room temperature and the contents were transferred to conical flask (500 mL) and kept in a refrigerator overnight. After this time, the water was decanted off and ethanol was added, and again kept in a refrigerator overnight. On the next day, ethanol was decanted off and acetone was added, and was again kept in a refrigerator for overnight. After this time, the starch was filtered and dried in an oven at 80 ºC for 10 h. The starch so obtained was expanded starch with more surface area. To a mixture of expanded starch (10 g) and 3-aminopropyl(trimethoxy) silane (1.79 g, 10 mmol), dry toluene (150 mL) was added in a round bottom flask and the reaction mixture was stirred under nitrogen atmosphere at 110 ºC for 24 h. The 3-aminopropyl starch (APS) was filtered, washed with toluene (200 mL) and ethanol (100 mL), and dried in a hot air oven at 80 ºC for 5 h. The yield of the 3-aminopropyl starch (APS) obtained was 9.5 g.

Preparation of ligand-grafted starch (imine)

To a mixture of 3-aminopropyl starch (8 g) and 2-acetylpyridine (0.968 g, 8 mmol) in a round bottom flask (250 mL), ethanol (150 mL) was added and the reaction mixture was refluxed under nitrogen for 24 h. After this time, the reaction mixture was cooled, filtered and the solid was washed with excess ethanol (150 mL) to remove the unreacted 2-acetylpyridine. Finally, it was dried at 80 °C in an oven for 5 h. The yield of ligand-grafted starch obtained was 7.5 g.

Preparation of starch-functionalized $Cu(OAc)_2$ [Star-$Cu(OAc)_2$]

Star-$Cu(OAc)_2$ was prepared by stirring a mixture of ligand-grafted starch (imine, 4 g) and $Cu(OAc)_2$ (0.920 g, 1.3 mmol/gm) in ethanol (60 mL) at room temperature under nitrogen atmosphere for 18 h. The solid was filtered off at pump and washed with acetone till washings were colourless. It was dried in an oven at 80 °C for 5 h and then conditioned for a total of 12 h (2 × 2 h each refluxing in acetonitrile, ethanol and toluene). The conditioned catalyst was dried under vacuum for 5 h before use. The yield of the Star-$Cu(OAc)_2$ was 3.5 g.

General procedure for the N-arylation of amines using phenylboronic acid catalyzed by Star-$Cu(OAc)_2$ at room temperature in acetonitrile

To a mixture of Amine (1 mmol), phenylboronic acid (1 mmol), K_2CO_3 (1 mmol) and Star-$Cu(OAc)_2$ (0.2 g, 3 mol% Cu) in a round-bottom flask (25 mL), acetonitrile (5 mL) was added and the reaction mixture was stirred at room temperature for an appropriate time (**Table 2**). After completion of the reaction (monitored by TLC), the reaction mixture was filtered and the residue was washed with acetonitrile (2 × 5 mL). The product was obtained after removal of the solvent under reduced pressure followed by crystallization or column chromatography. The catalyst was recovered from the residue after washing with methylene chloride (10 mL) followed by distilled water (200 mL) and then again with CH_2Cl_2. It was dried at 110 °C for 2 h and used further for carrying out the reactions

The structures of the products were confirmed by IR, ^1H NMR, ^{13}C NMR, mass spectral data and comparison with authentic samples available commercially or prepared according to the literature methods.

RESULTS AND DISCUSSION

The preparation procedure for starch functionalized copper(II) acetate [Star-$Cu(OAc)_2$] is outlined in **Fig. 1**. It involves the chemical modification by grafting a suitable ligand structure onto the surface of expanded corn starch, which was then treated with copper(II) acetate to give the starch-functionalized copper(II) acetate. Star-$Cu(OAc)_2$ was further conditioned for 12 h by refluxing each in acetonitrile (2 × 2 h), ethanol (2 × 2 h) and toluene (2 × 2 h) so as to remove the physisorbed copper(II) acetate.

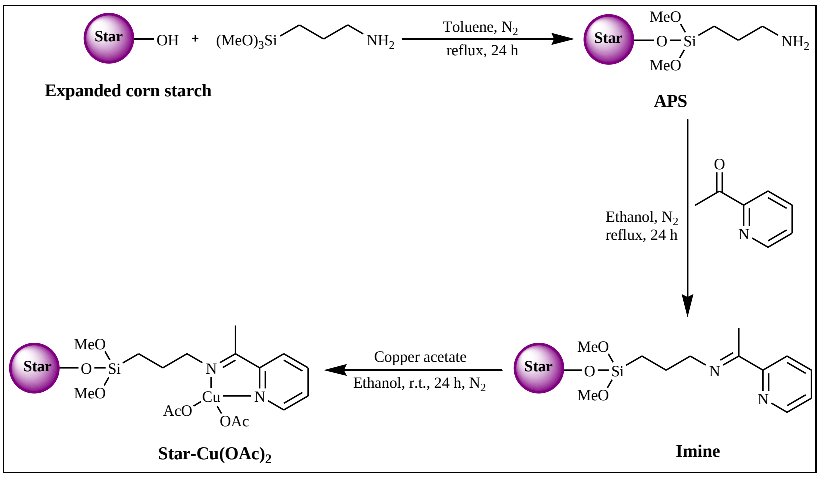


Fig.1 Preparation of starch functionalized copper(II) acetate [Star-$Cu(OAc)_2$]

FTIR

The FTIR of 3-aminopropyl starch displayed CH_2 stretching bands at 2925 and 2855 cm^{-1} and aliphatic deformation bands at 1457 and 1404 cm^{-1}. The FTIR of chemically modified starch (imine) showed a sharp peak at 1650 cm^{-1} due to C=N bond, which on complexation with $Cu(OAc)_2$ disappeared and appeared as a band at 1645 cm^{-1}. The lowering in frequency of the C=N peak is indicative of the formation of metal-ligand bond.

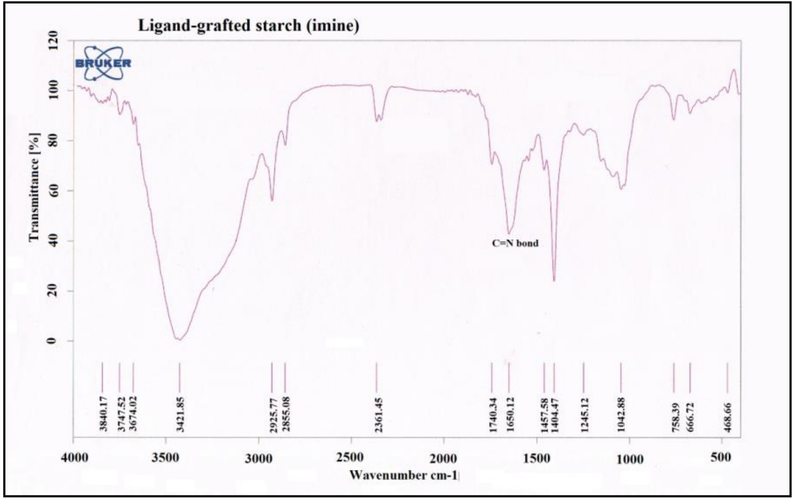


Fig.2 FTIR of ligand-grafted starch (imine).

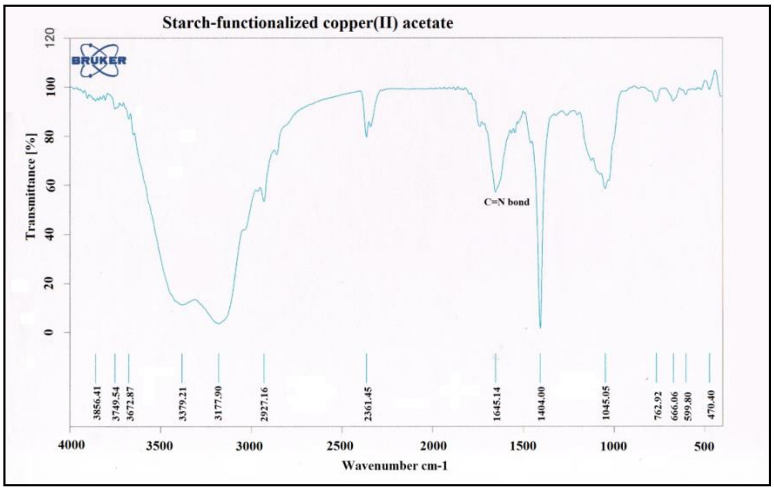


Fig. 3 FTIR of Star-Cu(OAc)$_2$.

Thermogravimetric analysis (TGA)

The stability of Star-Cu(OAc)$_2$ was determined by thermal analysis (TGA). TGA curve of Star-Cu(OAc)$_2$ showed an initial weight loss upto 100 °C which was due to loss the of residual solvent and water and then from 275 to 332 °C, which was due to the loss of organic functionality. Thus, the catalyst is stable up to 275 °C and it is safe to carry out the reaction at room temperature or 80-100 ºC.

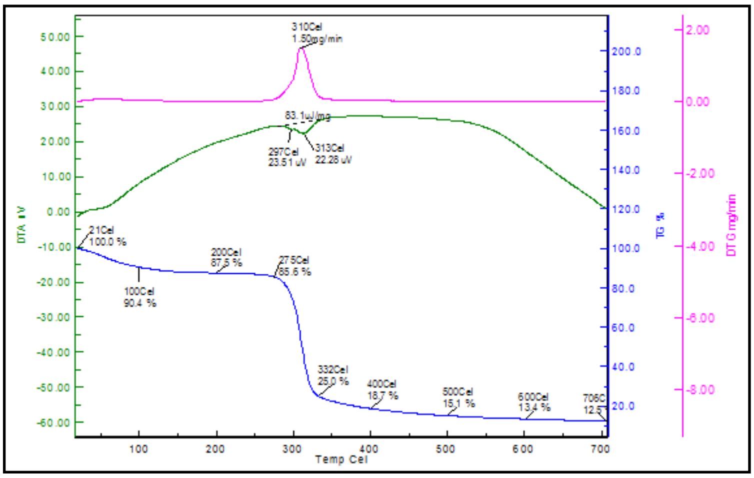


Fig. 4 TGA of Star-Cu(OAc)$_2$.

Atomic Absorption Spectrophotometric Analysis (AAS)

The amount of the copper loaded onto the surface of starch in Star-Cu(OAc)$_2$ was determined by AAS analysis. The catalyst was stirred in dil. HNO_3 and the solution was subjected to AAS analysis. Star-Cu(OAc)$_2$ was found to contain 0.009540 g of Cu per gram of the catalyst.

X-Ray Diffractometry (XRD)

The powdered X-ray diffraction patterns of Star-Cu(OAc)$_2$ showed the peaks in the pattern which were indexed on the basis of crystallographic data for the known structure of starch (**Fig. 5**). Three additional reflection patterns were obtained corresponding to $2\theta = 30.5^0$ (27.75), 35.6^0 (68.22) and 38.6^0 (97.37) which corresponds to Cu(OAc)$_2$$^{\mathbf{2}}$.

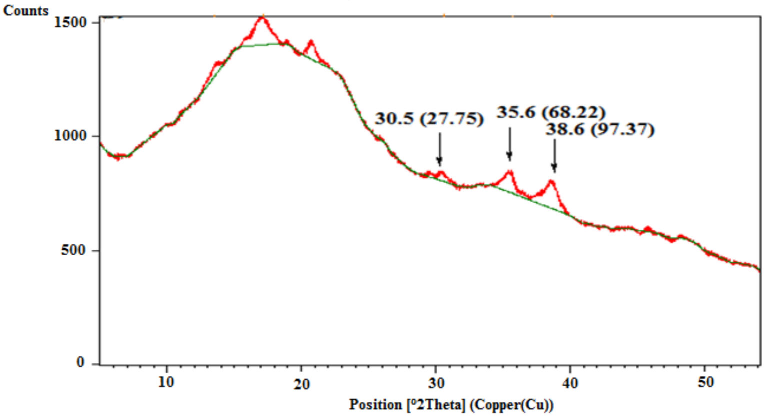


Fig. 5 XRD of Star-Cu(OAc)$_2$.

Scanning Electron Microscopy (SEM)

The microstructure and morphology of Star-Cu(OAc)$_2$ was studied using Scanning Electron Microscopy (SEM, **Fig. 6**). SEM image indicated that the complex has been successfully anchored onto the surface of starch and catalyst was found to be a homogeneous powder with porous structure.

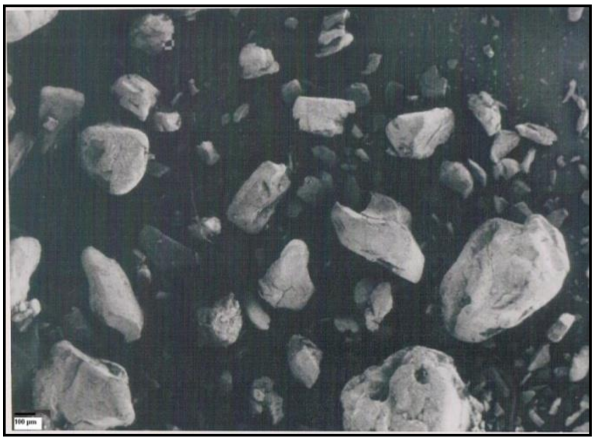


Fig. 6 SEM micrograph of Star-Cu(OAc)$_2$.

Transmission Electron Microscopy (TEM)

The TEM images (**Fig. 7**) shows the distribution of copper onto the surface of starch. From the image, it is clear that no bulk aggregation of the metal occurred indicating that copper is evenly distributed onto the surface of support material. In the TEM images, the copper nanoparticles are shown as dark spots of average diameter 7.8 nm.

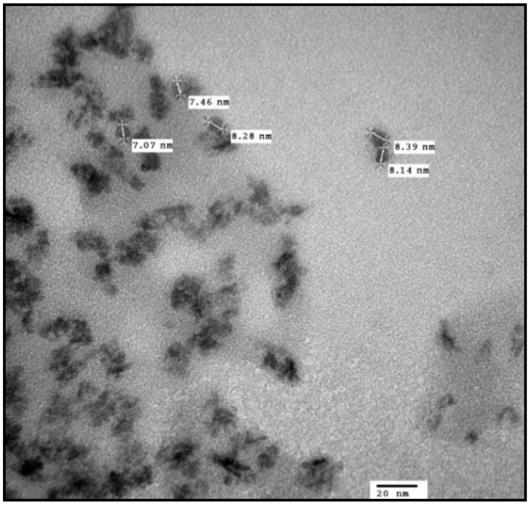


Fig. 7 TEM micrograph of Star-Cu(OAc)$_2$.

Catalyst testing for the N-arylation of amines with phenylboronic acid catalyzed by star-Cu(OAc)$_2$

Diaryl amines were prepared by stirring a mixture of phenylboronic acid and amine at room temperature in the presence of K_2CO_3 as base and Star-Cu(OAc)$_2$ as catalyst in acetonitrile (**Fig. 8**).

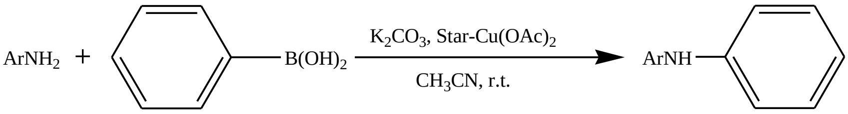
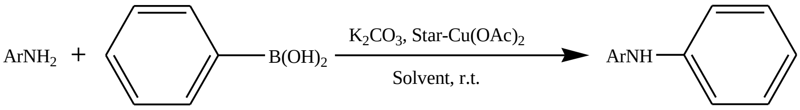


Fig. 8 Star-Cu(OAc)$_2$ catalyzed N-arylation of amines with phenylboronic acid in acetonitrile .

To optimize the reaction conditions, 4-bromoaniline was selected as the test substrate and N-arylation was carried out with phenylboronic acid using K_2CO_3 as base in various solvents like toluene, acetonitrile, ethanol and water (**Table 1**) at room temperature so as to achieve maximum selectivity for mono-*N*-substitution. The results in **Table 1** indicated that acetonitrile is the excellent reaction medium in terms of selectivity. Among various bases(K_2CO_3, Na_2CO_3, Cs_2CO_3) screened for the reaction, K_2CO_3 gave best results. Therefore, it was selected as the base of the reaction. Thus, the optimum conditions selected are: 4-bromoaniine (1 mmol), phenylboronic acid (1 mmol), K_2CO_3 (1 mmol), star-Cu(OAc)$_2$ (0.2 g, 3 mol% Cu), at room temperature and acetonitrile (5 mL) as the reaction medium.

Table 1. Effect of solvent on the Star-Cu(OAc)$_2$ catalyzed N-arylation of amines with phenylboronic acid at room temperature in different solvents[a]



Entry	Solvent	Time (h)	Yield (%)
1	Ethanol	24	55[b]
2	Methylene chloride	24	65[b]
3	Water	24	60[b]
4	**Acetonitrile**	**8**	**92**[c]

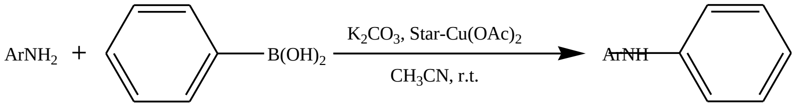
[a] Reaction conditions: 4-Bromoaniline (0.172 g, 1 mmol), phenylboronic acid (0.121 g, 1 mmol), K_2CO_3 (0.138g, 1 mmol), Starch-Cu(OAc)$_2$ (0.2 g, 3 mol% Cu) at room temperature in acetonitrile as solvent.

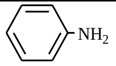
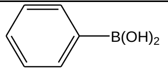
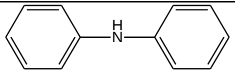
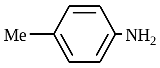
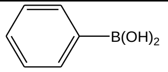
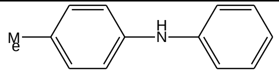
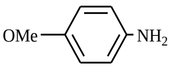
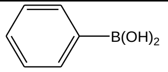
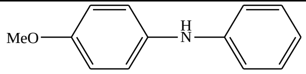
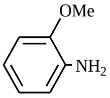
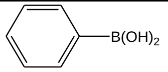
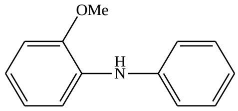
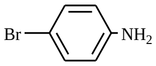
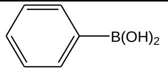
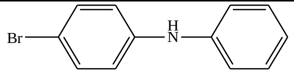
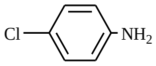
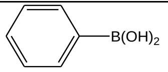
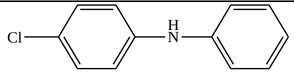
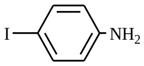
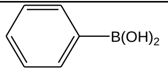
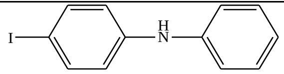
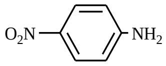
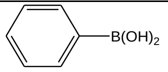
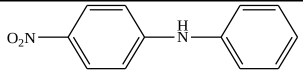
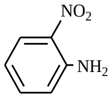
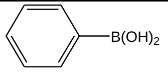
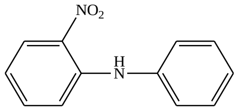
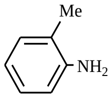
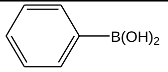
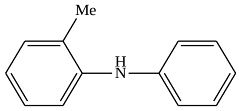
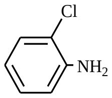
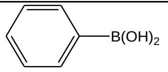
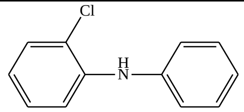
[b] Column chromatography yields.

[c] Isolated yields.

To survey the generality of this C–N coupling reaction, the scope and limitations of this protocol were examined using a series of primary aromatic amines under optimized reaction conditions (**Table 2**). From the results, it is clear that various arylamines, attached with either electron-donating or electron-withdrawing groups on the phenyl ring afforded the coupling products in good to excellent yields (**Table 2, entries 1–11**). Anilines with electron-rich groups were more favorable for the reaction under standard conditions. Moreover, para-Substituted anilines were found to be better substrates than ortho-substituted analogues (**Table 2, entries 2, 3,8 vs. 4, 9, 10**). These results show that the coupling reaction was slightly affected by steric congestion around the amino functionality of the aniline derivatives. The reaction was was also carried out using bromobenzene as halide but unfortunately very low conversion was observed (TLC).

Table 2. Star-Cu(OAc)$_2$ catalyzed N-arylation of amines with phenylboronic acid at room temperature in acetonitrile[a]



Entry	ArNH₂	Phenylboronic acid	Product	Time (h)	Yield (%)[b]
1				8	92
2				8	91
3				7	90
4				9	92
5				8	85[c]
6				8	91
7				8	91
8				12	85[c]
9				14	80[c]
10				10	90
11				10	88[c]

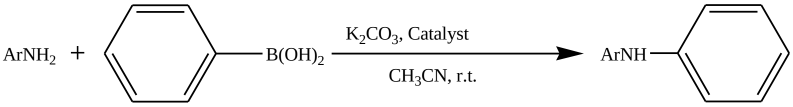
[a]Reaction conditions: Amine (1 mmol), phenylboronic acid (0.121 g, 1 mmol), K$_2$CO$_3$ (0.138g, 1 mmol), Starch-Cu(OAc)$_2$ (0.2 g, 3 mol% Cu) at room temperature in acetonitrile as solvent.

[b]Isolated yields.

[c]Column chromatography yields.

In order to find out the role of Star-Cu(OAc)$_2$ for the N-arylation of amines using phenylboronic acid, we have carried out the reaction in case of entry 5 (**Table 2**) with Cu(OAc)$_2$, APS, ligand-grafted starch (imine) and Star-Cu(OAc)$_2$. The reactions were also tested without Star-Cu(OAc)$_2$ under the similar conditions. The results are summarized in **Table 3** which clearly indicate that Star-Cu(OAc)$_2$ catalyzes the reaction and the corresponding diaryl amines was obtained in high yield and selectivity. It is pertinent to mention that reaction did not take place without any catalyst and with Cu(OAc)$_2$, the reaction was not selective, other side products were also formed.

Table 3. Effect of catalyst on N-arylation of amines with phenylboronicacid [a]



Entry	Catalyst	Time (h)	Yieldb (%)
1	No catalyst	24	NR
2	APS	24	NR
3	Imine	24	NR
4	Cu(OAc)$_2$	12	75[b]
5	**Star-Cu(OAc)$_2$**	**8**	**92[c]**

[a]Reaction conditions: 4-Bromoaniline (0.172 g, 1 mmol), phenylboronic acid (0.121 g, 1 mmol), K$_2$CO$_3$ (0.138g, 1 mmol), APS or imine (0.1 g), Cu(OAc)$_2$ (0.0054 g, 3 mol% Cu), Starch-Cu(OAc)$_2$ (0.2 g, 3 mol% Cu) at room temperature in acetonitrile as solvent.
[b]Column chromatography yields.
[c]Isolated yields.

Recyclability of the catalyst

For a heterogeneous catalyst, the deactivation and recycling of the catalyst are important issues to be resolved. To address these issues, we turned our attention to the reusability of Star-Cu(OAc)$_2$ in the N-arylation reaction of p-bromoaniline with phenylboronic acid under the same reaction conditions. After carrying out the reaction, the catalyst was collected by simple filteration and washed with acetonitrile and acetone and reused without further purification. From the results, it was shown that the catalyst retained its high catalytic activity over seven repeating cycles (Fig. 8). To cofirm whether the un-leached copper catalyst in the solution promoted the cross-coupling reaction, the following experiment was conducted. After suspending the star-Cu(OAc)$_2$ in acetonitrile overnight and then fltering off the catalyst, the cross coupling reaction of 4-bromoaniline and phenylboronic acid was performed in the filtrate. After 12 h, no conversion was observed on TLC.

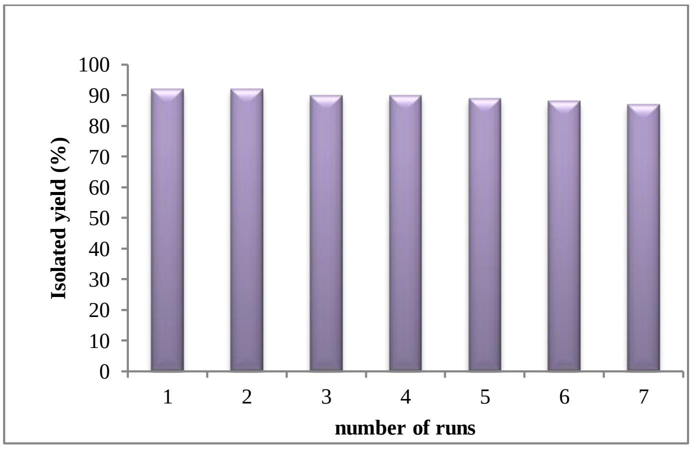


Fig. 8 Recyclability of Star-Cu(OAc)$_2$.

CONCLUSIONS

In conclusion, we have developed an efficient, and convenient protocol for the preparation of N-arylated amines by the coupling of arylboronic acids with amines in the presence of star-Cu(II) catalyst. Our inexpensive catalytic system showed a great functional group tolerance along with short reaction time and simple reaction conditions. Moreover, the star-Cu(II) catalyst can be collected easily by simple filteration and reused upto seven consecutive runs without significant loss of activity.

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