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N-Arylation of nitrogen heterocycles with aryl halides and arylboronic acids catalyzed by cellulose supported copper(0)

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Abstract

Cellulose supported copper(0) catalyst was prepared and employed for the *N*-arylation of nitrogen heterocycles with a variety of aryl halides and arylboronic acids to afford the corresponding coupled products in good to excellent yields without using external ligands or additives as promoters. The catalyst was recovered by simple filtration and reused for several cycles.

Keywords: Copper catalyst; Cellulose support; C–N coupling; Imidazole; Aryl halides; Arylboronic acids

1. Introduction

The metal mediated *N*-arylation is an important transformation in organic synthesis and the resulting arylated products have wide spread applications in pharmaceutical and agrochemical industries [1–6]. This reaction is generally achieved by the classical copper mediated Ullmann reaction under harsh reaction conditions utilizing stoichiometric quantities of copper salts and activated aryl halides as aryl donors. There are reports describing hypervalent iodonium salts [7], aryllead [8], arylbismuth [9], arylstannane [10] and arylsilane [11] as aryl donors using copper salts and a base. However, significant improvement in copper catalyzed *N*-arylations is realized after the introduction of arylboronic acids as the aryl donors, independently by Lam et al. [11c], Chan et al. [12] and Evans et al. [13] in 1998 utilizing stoichiometric amount of $Cu(OAc)_2$. More recently Collman et al. [14], Antilla and Buchwald [15] and Lam et al. [16] reported the catalytic version of *N*-arylation using arylboronic acids. Similarly, several copper catalyzed C–N coupling reactions under mild conditions have been reported using various ligands such as aliphatic-diamines [17], diimines [18], amido alcohols [19] and amino acids [20] as promoters using aryl halides as aryl donors. Most of the above methodologies are homogeneous in nature, where recyclability of the catalyst could not be achieved and moreover additional stabilizing ligand or co-oxidant is required.

We are interested to develop a supported copper catalyst, particularly utilizing naturally occurring biopolymer, cellulose, which is bio-degradable, environmentally safe, widely abundant in nature, inexpensive and easy to handle [21]. Cellulose and its derivatives are widely used in chemical and bio-chemical applications and also as supports for the synthesis of organic molecules [22]. Interestingly, it is also observed that cellulose fibers act as a nanoreactor for the stabilization of metal nanoparticles [23]. However, its use as a support for catalytic applications is not well explored. Recently, Quignard and Choplin reported cellulose as the support for water soluble $Pd(OAc)_2$/5TPPTS system in Trost Tsuji allylic alkylation reaction [24]. Similarly hydrogenation reactions with cellulose derivatives are reported [25]. Herein, we report *N*-arylation of imidazoles with arylboronic acids and aryl halides using cellulose supported Cu(0) catalyst (CELL-Cu(0)).

2. Experimental

2.1. Materials

Microcrystalline cellulose was purchased from S.D. Fine Chem. Ltd., India, and is used as such. $Cu(NO_3)_2{\cdot}3H_2O$ was purchased from LOBA Chemie, India. All the boronic acids, aryl halides and imidazole are purchased from Aldrich.

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2.2. Catalyst preparation

Microcrystalline cellulose (5 g) is added to a solution of 0.1 M (0.604 g) of $Cu(NO_3)_2{\cdot}3H_2O$ in distilled water (25 mL), and stirred for 15 min. Then, hydrazine hydrate (80%, 1 mL) is added drop wise for 15 min to the above reaction mixture and stirred for 12 h at room temperature. The grey coloured solid formed is filtered under nitrogen atmosphere, washed several times with distilled water, finally with acetone and dried under vacuum resulting cellulose supported Cu(0) catalyst.

2.3. Characterization

X-ray powder diffraction (XRD) data were collected on a Siemens/D-5000 diffractometer. The copper content in the supported catalyst was determined by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) using Thermo electron corporation make IRIS Intrepid 11 XDL instrument. X-ray photoelectronic spectrographs (XPS) are recorded on a KRATOS AXIS 165 instrument. All the products were characterized by ^{1}H NMR using Varian-Unity 400 MHz NMR Spectrophotometer.

2.4. Reaction procedures

2.4.1. General procedure for coupling of imidazole with arylboronic acids

To a mixture of imidazole (1 mmol), CELL-Cu(0) catalyst (0.025 g), triethylamine (2 mmol), in methanol (5 mL), arylboronic acid (1 mmol) was added and stirred under reflux. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with methanol. The solvent was evaporated under reduced pressure and followed a conventional work up with ethyl acetate and water. The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure to get the crude product. The crude product was purified by column chromatography (ethyl acetate:hexane) to afford the pure product, which gave satisfactory ^{1}H NMR and mass spectral data [14a,26].

2.4.2. General procedure for coupling of imidazole with aryl halides

To a mixture of imidazole (2 mmol), CELL-Cu(0) catalyst (0.05 g), K_2CO_3 (4 mmol), in DMSO (3 mL), aryl halide (2 mmol) was added and stirred at 130 °C for 24 h. The resulting reaction mixture was cooled to room temperature, filtered and followed a conventional work up with ethyl acetate and water. The organic layer was separated, dried over Na_2SO_4 and the solvent was removed under reduced pressure to get the crude product. The crude product was purified by column chromatography (ethyl acetate:hexane) to afford the pure product, which gave satisfactory ^{1}H NMR and mass spectral data [26,27].

3. Results and discussion

X-ray diffraction pattern of CELL-Cu(0) catalyst clearly indicates the presence of Cu(1 1 1) and Cu(2 0 0) phases which are attributed to Cu(0) (Fig. 1) [28]. Further, the high resolution XPS narrow scan (Fig. 2(a)) of the fresh CELL-Cu(0) catalyst shows a peak at 932.72 of Cu 2p3/2, which is attributed to Cu(0) [29]. ICP-AES analysis of the catalyst shows the presence of 0.368 mmol/g of copper.

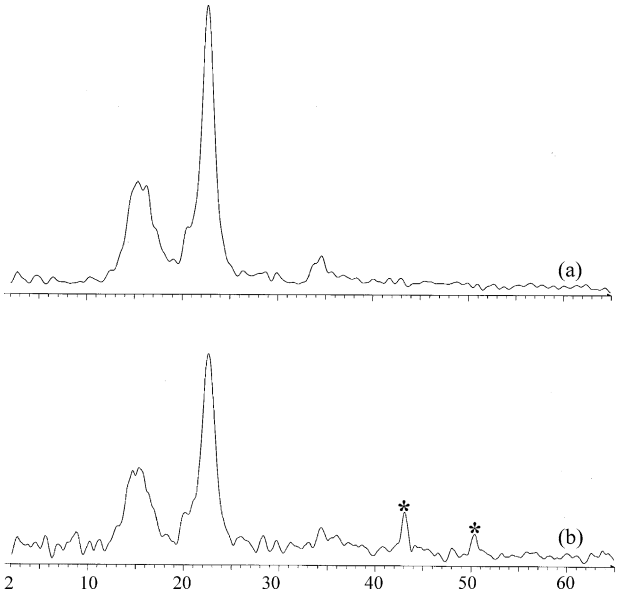


Fig. 1. X-ray diffraction patterns of: (a) microcrystalline cellulose and (b) CELL-Cu(0) catalyst.

Preliminary experiments are carried out by taking phenylboronic acid as a test molecule for the *N*-arylation of imidazole (Scheme 1). In order to determine the best reaction medium, we tested different solvents such as methanol, 1,2-dichloroethane, acetonitrile, tetrahydrofuran and toluene. Methanol is found to be the best solvent for the *N*-arylation of imidazole (98%). On the other hand, reaction in other solvents gave trace amount of coupled product under identical conditions. The nature of base has a pronounced effect in these reactions. Reaction of imidazole with phenylboronic acid in presence of K_2CO_3 and KO^{t}Bu gave no coupled product, while triethylamine and pyri-

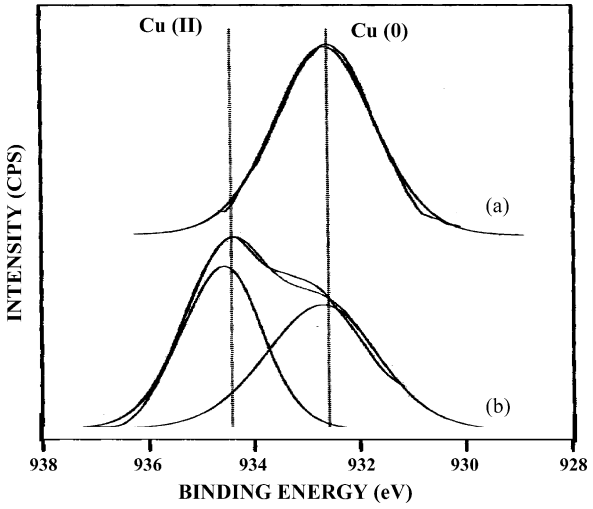
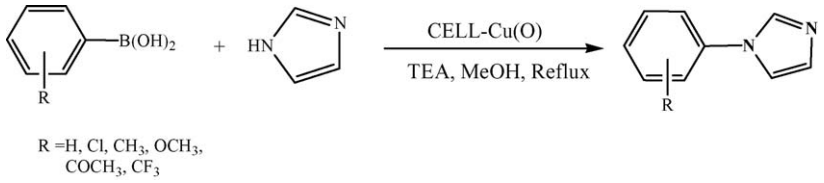


Fig. 2. XPS spectra of: (a) fresh and (b) used CELL-Cu(0) catalyst.



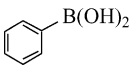
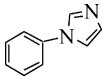
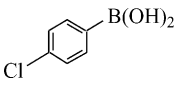
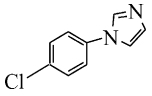
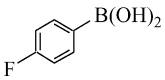
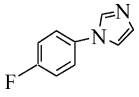
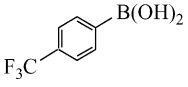
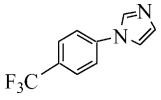
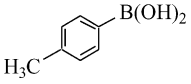
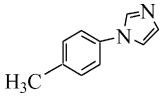
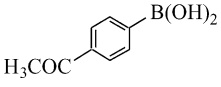
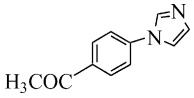
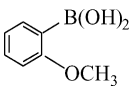
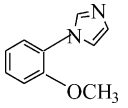
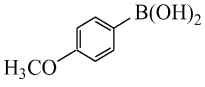
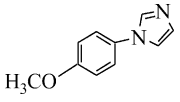
Scheme 1.

dine provided good yield. However, we continued the reactions in triethylamine instead of pyridine because of toxicity reasons.

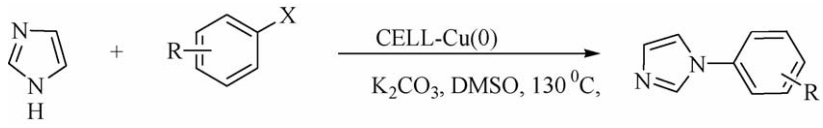
The reaction temperature plays an important role, the reaction at room temperature afforded 80% of the coupled product after 18 h (87%, 24 h), while the duration of the reaction is drastically decreased to 2.5 h under reflux conditions to provide quantitative yields (Table 1, entry 1).

After optimizing the reaction conditions, different arylboronic acids were coupled with imidazole using CELL-Cu(0) catalyst, triethylamine as base and methanol as solvent under refluxing conditions and the results are summarized in Table 1. Various structurally and electronically diverse arylboronic acids gave the corresponding *N*-arylated products in high yields. However, methyl, acetyl and methoxy substituted boronic acids required longer reaction times (Table 1, entries 5, 6 and 8) com-

Table 1
N-Arylation of imidazole with various arylboronic acids using CELL-Cu(0) catalyst[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			2.5	98
				87[c]
				80[d]
2			2.5	82
3			2.5	87
				83[c]
4			2.5	93
5			4.0	95
6			5.0	80
				77[c]
7			5.0	83
8			5.0	86

[a] Reaction conditions: imidazole (1 mmol), triethylamine (2 mmol), CELL-Cu(0) catalyst (0.025 g), phenylboronic acid (1 mmol), methanol (5 ml), reflux.
[b] Isolated yields.
[c] Yield after fourth cycle.
[d] Reaction performed at room temperature for 18 h.



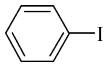
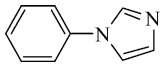
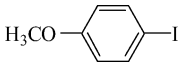
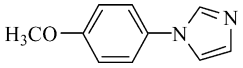
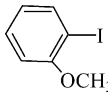
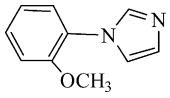
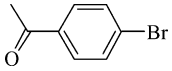
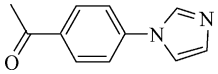
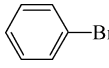
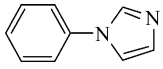
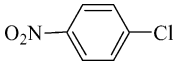
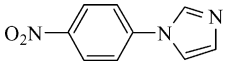
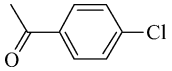
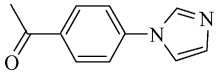
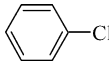
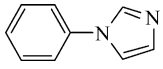
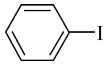
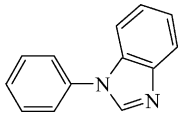
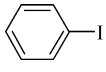
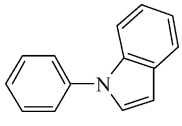
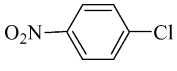
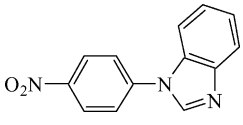
Scheme 2.

pared to chloro, fluoro and trifluoromethyl substituted boronic acids (Table 1, entries 2–4). *o*- and *p*-substituted arylboronic acids were equally effective for the coupling with imidazoles (Table 1, entries 7 and 8).

To explore further the applicability of this supported copper catalyst for C–N coupling reactions, we tested the *N*-arylation of imidazole with various aryl halides as aryl donors, which are less expensive than arylboronic acids using K_2CO_3 as base (Scheme 2).

In order to determine the best reaction medium, we tested different solvents such as methanol, 1,2-dichloroethane, toluene, DMF and DMSO for the *N*-arylation of imidazole with iodobenzene. DMSO is found to be the best solvent for the *N*-arylation of imidazole (95%) while DMF provided lower yield (15%). On the other hand, reaction in other solvents gave no coupled product under identical conditions. Temperature is proved to be very crucial, when the reaction is carried out at lower temperature (70 °C), <10% product formation was observed, by

Table 2
N-Arylation of nitrogen heterocycles with aryl halides using CELL-Cu(0) catalyst[a]

Entry	Aryl halide	Product	Time (h)	Yield (%)
1			12	95, 90[b], <10[c]
2			12	89(85)[b]
3			12	40
4			24	70
5			24	70
6			24	95(91)[b]
7			24	50
8			48	20[d]
9			24	40
10			24	60
11			24	85

[a] Reaction conditions: 2 mmol of aryl halide, 2 mmol of imidazole, 4 mmol of K_2CO_3, CELL-Cu(0) catalyst (0.05 g), DMSO, 130 °C.
[b] Yield after fourth cycle.
[c] Reaction temperature: 80 °C.
[d] Reaction with 0.1 g of CELL-Cu(0) catalyst.

raising the temperature to 130 °C quantitative (95%) yield of coupled product is achieved (Table 2, entry 1). Further experiments with different aryl halides were carried out under these optimized conditions and results are summarized in Table 2. Very good yield (89%) was observed for the reaction of imidazole with 4-iodoanisole (Table 2, entry 2). On the other hand, 2-iodoanisole resulted in lower yields, which may be because of steric factors (Table 2, entry 3). In the case of bromo-derivatives, 4-bromoacetophenone and bromobenzene afforded 70% of the coupled product (Table 2, entries 4 and 5). Further we have screened the chloro-derivatives (Table 2, entries 6–8) for the *N*-arylation of imidazole. Among them *p*-nitrochlorobenzene with a strong electron-withdrawing group resulted in quantitative yield (Table 2, entry 6), whereas 4-chloroacetophenone resulted in lower yield (Table 2, entry 7). *N*-Arylation of imidazole with chlorobenzene gave no coupled product under the above conditions. However, an increase of catalyst loading (0.1 g) with longer reaction time provided 20% yield of the coupled product (Table 2, entry 8). To test further the scope of this catalyst, reactions with benzimidazole and indole are conducted, which resulted in a very good yield (Table 2, entries 9–11).

We followed the *N*-arylation of imidazole with iodobenzene by GC at regular intervals of time during the reaction and the reaction profile is shown in Fig. 3. The conversion gradually increases with increase of time without the formation of any by-products.

3.1. Reusability of the catalyst

The catalyst was recovered by simple filtration and washed with acetone and oven dried. The recovered catalyst was reused for *N*-arylation of imidazole with different boronic acids (Table 1, entries 1, 3 and 6) and aryl halide (Table 2, entries 1, 2 and 6) derivatives. These results indicate that the CELL-Cu(0) catalyst can be used for several cycles successfully with minimal loss of activity. The high resolution XPS narrow scan (Fig. 2(b)) of the used CELL-Cu(0) catalyst shows two peaks at 932.72 and 935.25 of Cu 2p3/2, which are attributed to Cu(0) and Cu(II), respectively. ICP-AES results of the used CELL-Cu(0) catalyst indicate leaching of 0.8% of copper in the *N*-arylation reaction of imidazole with iodobenzene after the first cycle and 3.5% after the fourth cycle. In the reaction of imidazole with phenylboronic acid, leaching of 1.1% of copper after the first cycle and 5% after the fourth cycle are observed.

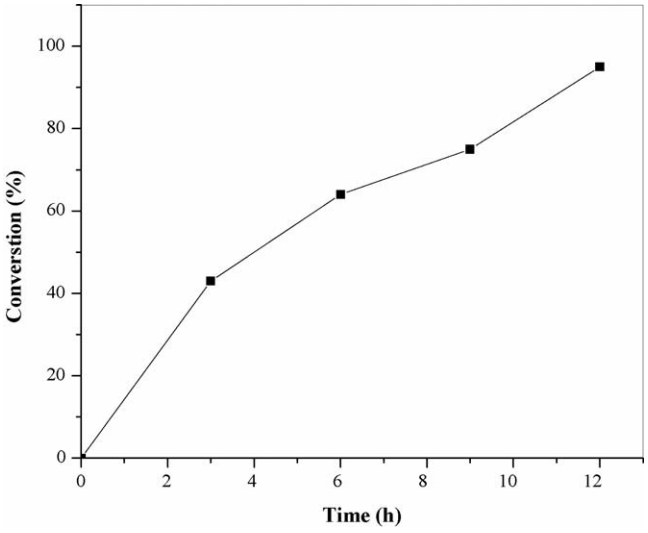


Fig. 3. Rate of change of conversion with time.

Hyeon and co-workers reported *N*-arylation of imidazoles with aryl chlorides using Cu_2O coated copper nanoparticles [28]. Rothenberg and co-workers described the synthesis of triazoles using copper nanoclusters and they reasoned that the surface of copper metal is usually coated by a monolayer of Cu(I) oxide, a dark red powder when in bulk, but virtually unnoticeable when on the metal, which may serve as the source of Cu(I) [30]. We assume that the present supported catalyst also contains Cu_2O coated copper nanoparticles. However, we could not see Cu_2O either in XRD or XPS because of low concentration of Cu_2O.

4. Conclusions

In conclusion, cellulose supported copper catalyst was prepared and employed for the *N*-arylation of nitrogen heterocycles with a variety of aryl halides and arylboronic acids to afford corresponding coupled products in good to excellent yields without using any external ligands or additives as promoters. The catalyst was recovered by simple filtration and reused for several cycles.

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