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Recyclable heterogeneous copper oxide catalyzed synthesis of phenols at room temperature under ligand-free conditions

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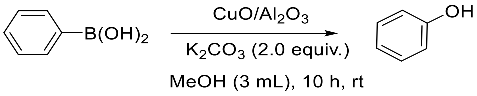
Abstract

An efficient Alumina supported CuO catalyzed synthesis of phenols from various arylboronic acids in presence of K_2CO_3 under ligand free condition is reported. This protocol provides a variety of differently substituted phenols by a simple straightforward and efficient methodology in good yields. The explored catalyst is inexpensive, air-stable and recyclable up to three cycles.



Keywords: boronic acids, phenols, CuO/Al_2O_3 catalyst, heterogeneous catalyst, recyclability

1. Introduction

Phenols serve as synthetic building blocks as well as versatile synthons in preparing oxygenated heterocycles [1, 2] and are very important intermediates in the chemical, pharmaceutical and material industries. These occur abundantly in nature as constituents in coal tar, amino acids, flavonoids, tannins and hormones (Figure 1) [2]. Simple phenols as well as poly phenols are found to be effective disinfectants [3]. Phenol and its derivatives are traditionally synthesized either by the nucleophilic substitution reaction of activated aryl halides or by the copper-catalyzed transformation of diazirines [4]. However, these methods generally suffer from limitations such as the harsh reaction conditions [5] as well as expensive catalysts.

Recently, several palladium catalyzed processes have allowed the cross-coupling of aryl halides with hydroxide salts to proceed under milder conditions [6]. Buchwald and co-workers reported reactions with catalyst systems derived from Pd_2dba_3 and phosphine ligands providing an effective route for the preparation of phenols from neutral, electron-rich, *ortho*-substituted and functionalized aryl/heteroaryl bromides and chlorides [7]. Beller *et al.* developed a practical imidazole-based phosphine ligands for selective palladium-catalyzed hydroxylation of aryl halides [8]. However, these palladium catalyzed reactions have certain limitations such as high cost of palladium salts, phosphine ligands and tedious synthetic procedures.

The economic viability of copper as an effective catalyst has led to a remarkable progress in the development of copper-catalyzed coupling reactions [9], such as the copper mediated hydroxylation of aryl halides with hydroxide salts (like KOH and NaOH) as nucleophiles to form phenols under milder reaction conditions. Wang *et al* reported the direct catalytic hydroxylation of arylboronic acids to phenols by using simple copper salts and 1,10-phenanthroline in the presence of KOH as a base at room temperature in water [10]. Taillefer *et al* described a selective hydroxylation process for both activated and unactivated aryl bromides and iodides in aqueous medium in the presence of a metal hydroxide and a copper catalytic system along with simple diketone ligands [11]. Fu *et al* developed a simple, practical and efficient copper-catalyzed synthesis of substituted phenols from aryl halides by using environ friendly water as a solvent medium under mild conditions [12]. Jingson You and co-workers reported the synthesis of phenol derivatives from aryl halides by coupling with potassium hydroxide under simple reaction conditions, in the presence of CuI and 1, 10-phenanthroline (phen), an inexpensive and commercially available ligand [13]. These copper catalyzed reactions also involve drawbacks, such as the use of stoichiometric amounts of the catalyst, high reaction temperatures and lack of recyclability.

The heterogeneous catalysts are economically more attractive than homogeneous catalysts. Moreover, in the realm of cross-coupling reactions, metal anchored heterogeneous supported reagents gained prominence in the recent past, in view of their advantages like improved efficacy due to the presence of numerous stable active sites, easy product purification. Diaconescu demonstrated that palladium nanoparticles supported on polyaniline nanofibers as a semi-heterogeneous catalyst in water for the synthesis of phenols from aryl halides and potassium hydroxide [6a]. Furthermore, the nanoscale catalysts are more advantageous as more active surface area is available to bind the substrates selectively and enhance the reaction efficiency [16]. Very recently Xu and Feng reported that the CuI in the form of nanoparticle catalyzed selective synthesis of phenols from aryl halides in aqueous solution.[9d] However, a literature survey reveals that copper-catalyzed synthesis of phenols from aryl halide and base has only a few reports with recovery of the catalyst. Here in we describe a simple, efficient and recyclable catalytic system for the synthesis of phenols, by an oxidative hydroxylation of arylboronic acids, employing hydroxide salts under ligand-free conditions.

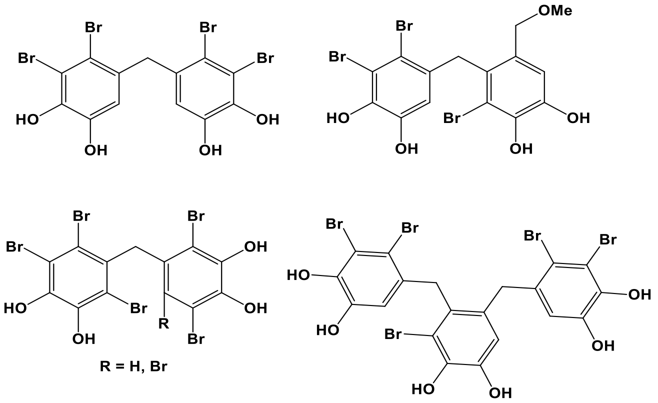


Fig 1: Some of the biologically active bromo phenols.

2. Results and Discussion

As a part of our continuous research interest in the field of heterogeneous catalysis [14], the role of inexpensive CuO on alumina, as a recyclable catalyst was investigated for the first time in the synthesis of phenol and its derivatives. Initially, a reaction was performed with arylboronic acid [1a] and K_2CO_3in the presence of CuO/Al_2O_3 catalyst at room temperature in MeOH for 10 h to provide the corresponding product [2a] in 90% yield. The reaction parameters such as solvent, base and catalyst loadings were optimized during the preliminary studies. The influence of different solvents such as MeCN, DMSO, DMF, MeOH and H_2O was examined (entries 1 - 5, Table 1), and MeOH was found to be the most efficient solvent for this reaction affording the best yield of phenol (entry 4, Table 1). Among various bases tested, K_2CO_3 was observed to be more efficient than other bases such as Cs_2CO_3, *t*-BuOK and NaOH (entries 1 - 4, Table 2).

Several copper catalysts were also screened for their influence on the synthesis of phenols and the results are summarized in Table 3. No product formation was observed in the absence of any copper catalyst (entry 1, Table 3). The heterogeneous CuO/Al_2O_3 produced phenol [2a] in an impressive yield compared to other catalysts such as $CuSO_4$, CuBr, Cu_2O, CuO, $Cu(OAc)_2$ and CuCl (entries 2 - 8, Table 3). Moreover, their catalytic activities were lower than CuO/Al_2O_3 system (entry 6, Table 3). The optimal reaction conditions observed for the synthesis of phenols employing hydroxide salts were CuO/Al_2O_3 (150 mg, 13 wt %), 2.0 equiv of K_2CO_3 and MeOH as a reaction medium 3 mL, at room temperature.

While exploring the scope of the reaction, various arylboronic acids were subjected to hydroxylation process by employing hydroxide salts in the presence of heterogeneous CuO/Al_2O_3 catalyst under ligand-free conditions. In general, all the reactions were simple, very clean and the phenol and its derivatives were obtained in high yields under optimized conditions. The substitutions on arylboronic acid at different positions played a major role in governing the reactivity of the substrate. The arylboronic acids containing electron withdrawing groups at *para*-position afforded higher yields compared to those with electron donating groups at *para*-position and the results are summarized in Table 4. Sterically demanding *ortho*-substitution hampered the reaction and led to the formation of the products in lower yields (entries 14-15, Table 4). Satisfactory yields were obtained in the case of arylboronic acids containing substitutions at *meta*-position (entries 16 - 17, Table 4).

Further the reusability of the heterogeneous CuO/Al_2O_3 was studied in the hydroxylation of arylboronic acids. After completion of the reaction, the catalyst was recovered by centrifugation and washed with water followed by acetone, then dried in vacuum and used directly for further catalytic reactions. No significant change in the efficacy was observed up to three cycles.

After separation, the solid catalyst was checked by XPS and SEM techniques and it was found that there was no change in the nature of the catalyst before and after the reaction. The X-ray photoelectron spectroscopic (XPS) study [15], of the fresh and used CuO/Al_2O_3 catalyst at the Cu 2p level shows the $2p_{3/2}$ lines at 934.5 and 934.6 eV and the Cu 2p level shows the $2p_{1/2}$ lines at 954.6 and 954.8 eV respectively, which indicates that Cu is in the +2 oxidation state before and after the reaction (Figure 2). The SEM images of the CuO/Al_2O_3 catalyst before and after the cycles were recorded and it was observed that the morphology and size of the catalyst did not change considerably, even after the last cycle (Figure 3). The above experimental results clearly suggest that there was no significant change in the oxidation state and catalytic activity of CuO/Al_2O_3 catalyst before and after the reaction.

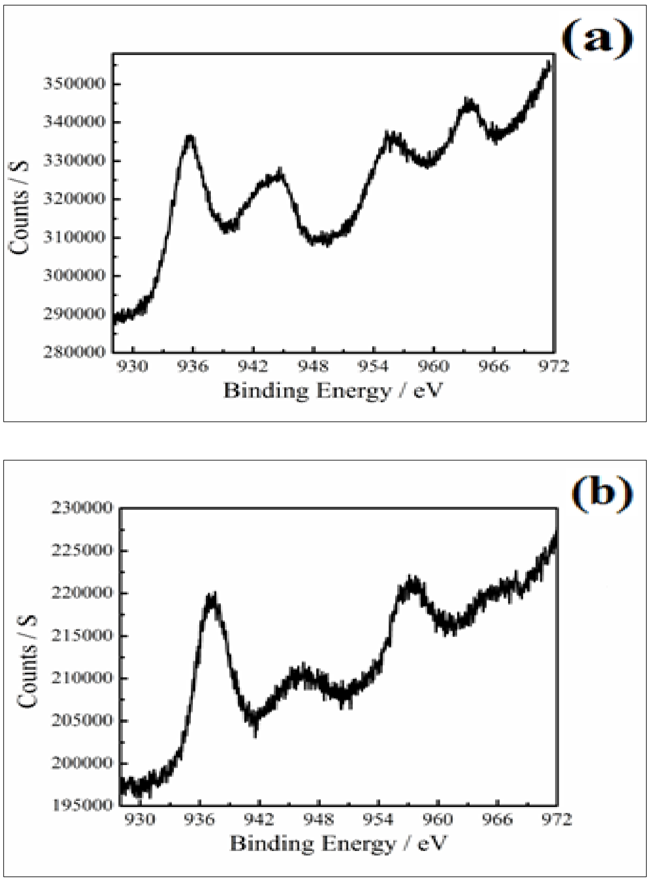


Fig 2: XPS profiles of (a) Cu 2p orbital of native CuO/Al_2O_3 catalyst (b) Cu 2p orbital of reused CuO/Al_2O_3 catalyst.

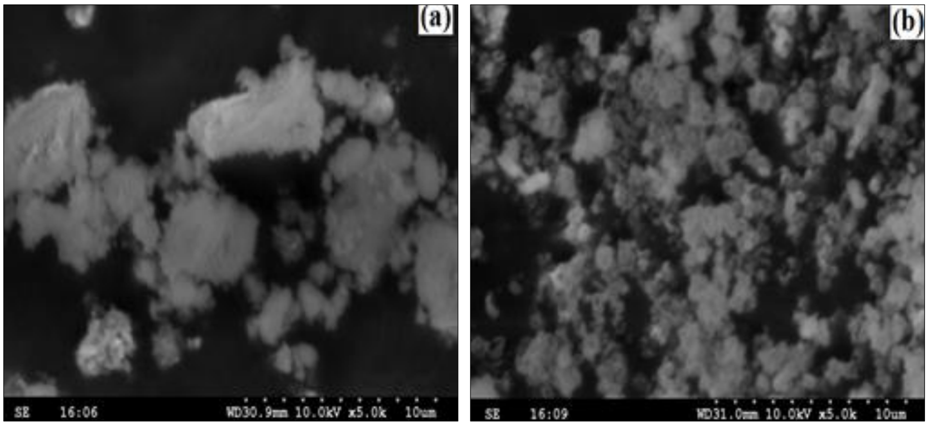
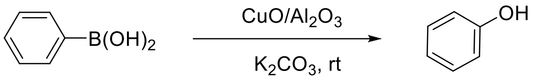


Fig 3: SEM images of heterogeneous CuO on alumina catalyst (a) native catalyst and (b) *reused catalyst.*

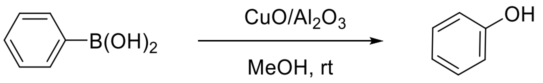
Table 1: Solvent optimization studies.[a]



Entry	Solvent	Yield (%)[b]
1	MeCN	49
2	DMSO	50
3	DMF	49
4	MeOH	90
5	H_2O	49

[a] Reaction conditions: Arylboronic acid (1mmol), cuo?Al_2 O_3 (150 mg, 13 wt%), K_2 CO_3 (2.0 equiv.), solvent (3mL), rt, 10h.[b] Isolated yield

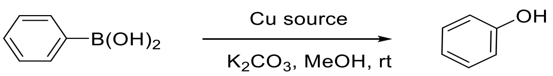
Table 2: Efficacy of different based on hydroxylation of arylboronic acids.[a]



Entry	Base	Yield (%)[b]
1	Cs_2CO_3	45
2	*t*-BuOK	30
3	K_2CO_3 (2.0 equiv.)	90
4	NaOH	50

[a] Reaction conditions: arybooronic acid (1mmol), CuO/Al_2 O_3 (150mg, 13wt%), base (2.0 equiv.), MeOH (3mL), rt, 10h.[b] lsolted yield.

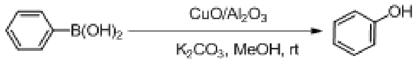
Table 3: Catalytic efficiency of different Cu sources on the hydroxylation of aryboronic acids. Arylboronic acids. [a]

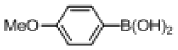
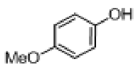
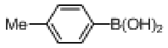
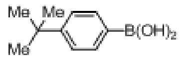
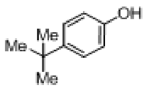
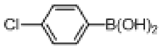
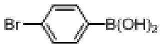
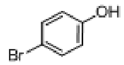
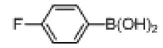
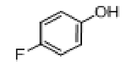
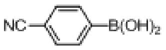
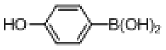
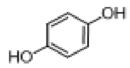
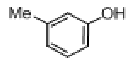
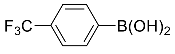
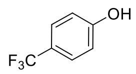
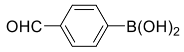
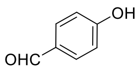
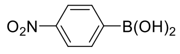
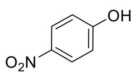
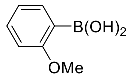
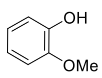
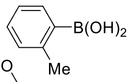
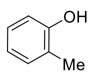
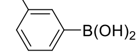
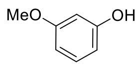
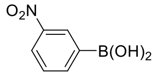
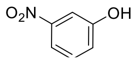


Entry	Catalyst	Yield (%)[b]
1	-	-
2	$CuSO_4$	73
3	CuBr	71
4	Cu_2O	75
5	CuO	79
6	CuO/Al_2O_3	90
7	$Cu(OAc)_2$	60
8	CuCl	68

[a] Reaction conditions: Arylboronic acid (1 mmol), Cu source, K_2CO_3 (2.0 equiv.), Meoh (3ml), rt, 10h.[b] Isolated yield

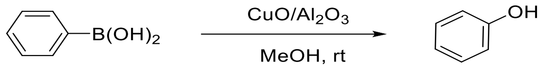
Table 4: Synthesis of phenols using heterogeneous copper oxide on alumina as a Catalyst.[a]



Entry	Arylboronic acids	Product		Yield (%)[b]
1			2a	90
2			2b	80
3			2c	78
4			2d	75
5			2e	85
6			2f	80
7			2g	85
8			2h	84
9			2i	78
10			2j	75
11			2k	82
12			2l	81
13			2m	86
14			2n	65
15			2o	68
16			2p	76
17			2q	75

[a] Reactions conditions: Arylboronic acid (1 mmol), CuO/Al_2O_3 (150 mg, 13wt%), K_2CO_3 (2.0 equiv.), MeOH (3ml), rt, 10h. [b] Isolated yield

Table 5: recovery of catalyst>^{a}



Cycle	Product isolated yield (%)	Catalyst recovery (%)
native	90	93
1	85	91^b
2	83	88^b
3	79	80^b

Reaction conditions: arylboronic acid (1mmol), k2co3 (2.0 equiv.), MeOH (3ml), rt, 10 h. ^{B} with recovered catalvst.

Conclusions

In conclusion, a general and efficient preparation of phenols was developed by a CuO/Al_2O_3 catalyzed oxidative hydroxylation of arylboronic acids at room temperature in methanol under ligand free conditions. To the best of our knowledge, this is the first report of a simple protocol for the synthesis of phenols catalyzed by heterogeneous recyclable copper oxide on alumina by the oxidative hydroxylation of arylboronic acids.

Experimental section

- **General Information:** Arylboronic acid (99%), CuO on Alumina (99.9%) were purchased from Sigma Aldrich and used without purification. Column chromatography was carried out with 60-120 sized mesh silica gel using ethyl acetate and hexane as eluents. Analytical TLC was performed with Merck silica gel 60 F_{254} plates, and the products were visualized by UV detection. ^1H NMR and ^{13}C NMR (Avance 300, Innova 400 MHz and Brucker Gemini 200 MHz) spectra were recorded in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) were reported in ppm, and spin-spin coupling constants (J) are in Hz. Melting points were determined on a Fischer-Johns melting point apparatus. EI-MS were recorded on a Finnegan MAT 1020 mass spectrometer operating at 70 eV.
- **Representative experimental procedure for the synthesis of phenol by using CuO/Al_2O_3 as a catalyst:** Arylboronic acid was mixed with K_2CO_3 (2.0 equiv.) and CuO/Al_2O_3 catalyst (13wt%, 150 mg) in MeOH (3.0 mL) and the reaction mixture was stirred at room temperature under air for 10 h, The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3x10 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give the crude product, which was purified by column chromatography with ethyl acetate/ hexane as an eluent to yield the expected product [2a] (85 mg, 90%) as a colorless oil. The purity of the product was confirmed by ^1H, ^{13}C and mass spectroscopy.
- **Representative procedure for recycling:** After extraction of the organic compounds with ethyl acetate, the recovered heterogeneous catalyst was placed in a 25 mL round-bottomed flask. Aryl boronic acid [1a] (1.0 mmol) and K_2CO_3 (2.0 equiv.) were added under air, followed by addition of MeOH (3.0 mL) and the reaction mixture was stirred at room temperature for 10 h. After completion of the reaction (as monitored by TLC), the heterogeneous mixture was then cooled to room temperature and treated with ethyl acetate (2 mL). The aqueous layer was separated and extracted with ethyl acetate (3x5 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the product, which was purified by column chromatography using silica gel (ethyl acetate/hexane) to obtain the pure product **[2a]** (80 mg, 85%) as a colorless oil. The product was characterized by ^1H and ^{13}C NMR, and MS analysis and compared with the literature values. The same procedure was extended for further cycles.
- **Phenol [11] (2a) (entry 1, Table 4):** 90%, Colorless oil, ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 - 7.16 (m, 3H), 6.91 - 6.83 (m, 1H), 6.81 - 6.74 (m, 2H), 5.11 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 129.6, 120.7, 115.3. EI-MS: 94.

Supporting information

Supporting Information: Full experimental detail, ^1H, ^{13}C NMR, FT-IR and Mass spectral data of phenol and its derivatives. This material can be found in the “Supporting Information” section of this article.

Acknowledgements

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