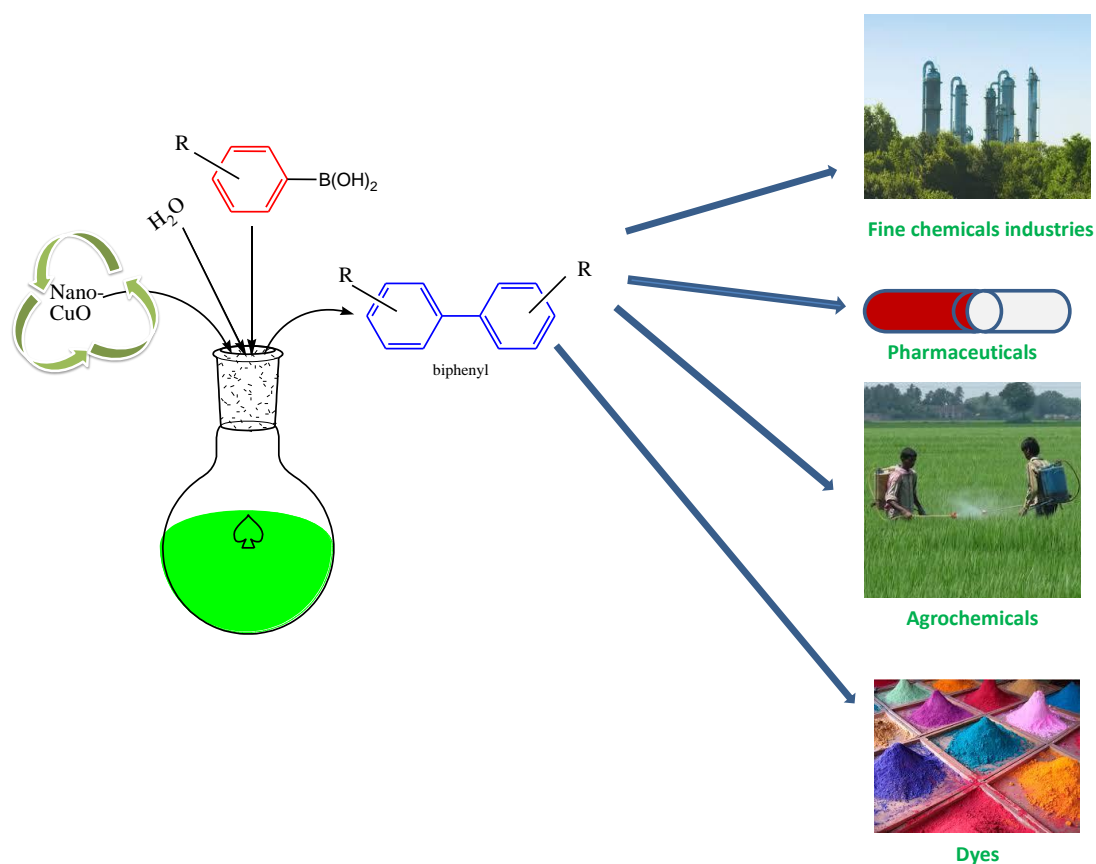


Chapter 3

In water homocoupling of arylboronic acid using nano-rod shaped and reusable copper oxide(II) catalyst at room temperature



Chapter 3

3.1 Introduction

One of the important discoveries in the domain of synthetic organic chemistry is the coupling reactions for the formation of carbon-carbon bonds. Specifically, the coupling products, symmetrical and unsymmetrical biaryls are in huge demand in pharmaceutical, natural product synthesis and fine chemicals industries¹⁻⁷ as they are found to exhibit a variety of physical and chemical properties⁸ with versatile applications as dyes, agrochemicals, semi-conductor and optically active ligands⁹ and drugs.¹⁰

Now-a-days, developing environmental friendly methodologies for the preparation of biaryls is one of the most important and interesting topics. Recently, aerobic homocoupling of phenylboronic acid has attracted much attention among researchers.¹¹⁻¹⁴ Generally, synthesis of symmetrical and unsymmetrical biaryls has been achieved by transition-metal-catalyzed couplings such as the Suzuki reaction,¹⁵ modified Ullmann reaction,¹⁶ Kumada–Corriu–Tamao reaction,¹⁷ etc. Recently, many researchers have reported oxidative homocoupling of arylboronic acids as an excellent method to obtain symmetrical biaryls as arylboronic acids prepared from the corresponding aryl halides are more stable and less toxic than many other organometallic reagents. Palladium-based catalysts are frequently used for the homocoupling of arylboronic acids.¹⁸⁻²⁰ However, there are some limitations in these catalytic methods, e.g. (1) Palladium is expensive and additional ligands are usually required,²¹ (2) certain oxidants are employed to regenerate the catalyst,²² (3) addition of a strong base is required to achieve high yields of biaryls,²³ and (4) requirement of high temperature to complete the reaction.²⁴ Therefore, there is need and scope for improvement. Many studies have shown that metals like Au,²⁵ Rh,²⁶ Ni²⁷ and Cu²⁸ can also catalyze the homocoupling of arylboronic acids. But, the above mentioned metal catalysts have some drawbacks such as requiring long reaction time, economically costly, lack of reusability and environmentally not friendly. Au and Rh are expensive and some additives are necessary for catalysis.^{25,26} Pungent pyridine is generally used as solvent in Ni catalytic system with heating required.²⁷

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It is reported that the homocoupling of arylboronic acids can be carried out in DMF in the presence of $\text{Cu}(\text{OAc})_2$ without any additive such as a ligand.²⁸ However, this reaction requires a harsh condition with high temperature (100 °C). Yamamoto *et al* reported that the homocoupling of arylboronic acids could be catalyzed by a copper complex containing 1,10-phenanthroline as ligand.²⁹ Pitchumani and co-workers have reported that copper terephthalate metal–organic frameworks can be used to mediate the homocoupling of arylboronic acids.³⁰

Recently, some researchers have reported that NPs could be successfully used as catalyst to enhance the speed of a reaction in order to achieve more yield and less bi-products.³¹ We have reported earlier that basic nano Al_2O_3 catalyst could be used for the *N*-formylation reaction under NOSE approach.³² These applications seem to be motivated by the intention to enhance the catalytic efficiency through large surface areas of the NPs. However, a more intriguing aspect of the NP catalysis arises from their size-specific electronic and geometric structures. Till now, to the best of our knowledge there is no report of use of CuO nanocatalyst to enhance the synthesis of biphenyls. In this paper, we report an easy and efficient nano CuO catalyzed homocoupling reaction of arylboronic acids for the synthesis of symmetrical biaryls under mild conditions without the need of any additives. Here, CuO nanorod is synthesized as reported earlier by our group³³ in a very efficient, environment friendly wet chemical process and well characterized.³³

3.2 Experimental Section

Representative procedure for the CuO NPs catalyzed homocoupling of arylboronic acid

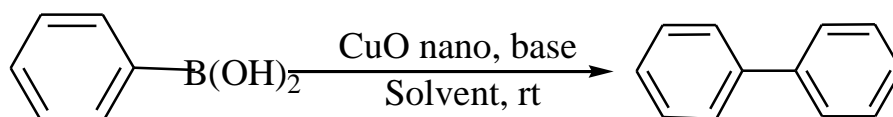
A solution of nano CuO (0.010 mmol) and substituted phenylboronic acid (0.75 mmol) in H_2O (2 mL) was stirred at 25 °C for 2h under aerobic condition. After the reaction was over, the reaction mixture was extracted with ethyl acetate and washed with double distilled water in a separating funnel. The organic layer was separated and collected in a conical flask. After evaporation of the solvent in a rotary evaporator, reaction mixture was subjected to column chromatography on silica gel column (ethyl acetate/hexane, 1:10) to afford the respective product.

3.3 Results and discussion

3.3.1 Characterisation and homo-coupling reaction

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In this paper, we report the heterogeneous nano CuO catalysed homocoupling of arylboronic acids in air at room temperature (rt). In all the cases, it is found that nano CuO is an efficient and environmentally-friendly heterogeneous, reusable catalyst. Optimization of reaction conditions has been carried out taking same amount of the catalyst. Initially, phenylboronic acid was selected as a model substrate with variation of solvent (Scheme 3.1) as well as base with the aim of optimizing the yield and the results are summarized in Table 3.1. All reactions were conducted at rt under aerobic condition. Very less amount of product was found in the absence of a base (Table 3.1, entries 1-3).



Scheme 3.1: Model reaction for synthesis of biphenyls

Table 3.1: Optimization of the reaction condition for solvent, time and base^a

Entry	Catalyst (20 mol%)	Solvent (2 mL)	Base (0.5 eqv.)	Time (hr)	Yield ^b (%)
1	CuO	MeOH	Nil	36	20
2	CuO	<i>i</i> -PrOH	Nil	36	30
3	CuO	H ₂ O	Nil	36	34
4	CuO	MeOH	K ₂ CO ₃	1.5	79
5	CuO	MeOH	CS ₂ CO ₃	1.5	84
6	CuO	MeOH	Na ₂ CO ₃	1.5	64
7	CuO	<i>i</i> -PrOH	K ₂ CO ₃	2	91
8	CuO	H ₂ O	K ₂ CO ₃	4	96
9	CuO	H ₂ O	K ₂ CO ₃	3	96
10	CuO	H ₂ O	K ₂ CO ₃	2	96
11	CuO	H ₂ O	K ₂ CO ₃	1	86
12	CuO	H₂O	K₂CO₃	1.5	95

^aReaction condition: Phenylboronic acid (1 mmol), solvent (2 mL), base (0.5 eqv.)

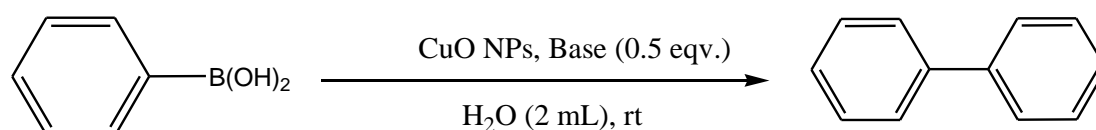
^bIsolated yield

The reaction was performed with different alkaline bases in methanol solvent at rt and yield of the biphenyls has been increased in case of K₂CO₃ base. Keeping K₂CO₃ fixed, different solvents were used and best result was obtained in case of water. Again, the reaction was subjected to time variation in presence of K₂CO₃ and

water in order to get optimization reaction time. 96% product was formed in presence of K_2CO_3 , and CuO catalyst at rt in water within 1.5 hours (Table 3.1; Entry 12).

The biphenyls yield was also found to increase rapidly with an increase in the amount of catalyst. We have taken CuO catalyst in mol% and it was found that as the amount of catalyst was increased to 10 mol%, biphenyls was formed in highest yield and the further addition of catalyst had no obvious effect on the yield of biphenyls (Table 3.2).

Table 3.2: Optimization of reaction condition for the catalyst^a



Entry	Catalyst	mol%	Solvent	Base (0.5 eqv.)	Time (h)	Yield ^b (%)
1	CuO	20	H ₂ O	K ₂ CO ₃	1.5	96
2	CuO	17	H ₂ O	K ₂ CO ₃	1.5	96
3	CuO	15	H ₂ O	K ₂ CO ₃	1.5	95
4	CuO	12	H ₂ O	K ₂ CO ₃	1.5	95
5	CuO	10	H₂O	K₂CO₃	1.5	95
6	CuO	9	H ₂ O	K ₂ CO ₃	1.5	89
7	CuO	8	H ₂ O	K ₂ CO ₃	1.5	81
8	CuO	7	H ₂ O	K ₂ CO ₃	1.5	75
9	CuO	5	H ₂ O	K ₂ CO ₃	1.5	47
10	CuO	3	H ₂ O	K ₂ CO ₃	1.5	23

^aReaction condition: Phenylboronic acid (1 mmol), solvent (2 mL), base (0.5 eqv.)

^bIsolated yield

Thus, homocoupling of arylboronic acids was performed taking CuO nanorod as catalyst in water under air for 1.5 h at room temperature. It is noteworthy to mention that CuO NPs were synthesized in wet chemical process as per our earlier report³³ and well characterized with the help of TEM, SEM, EDAX and XRD. From TEM analysis it is clear that the particle is of nanosize (Figure 3.1). SEM and EDAX of nano CuO are shown in Figures 3.2 and 3.3 respectively.

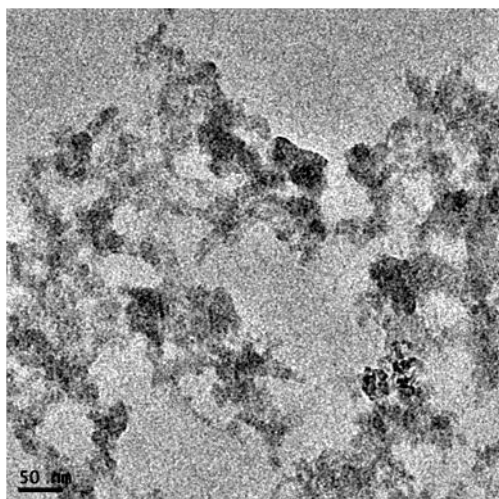


Figure 3.1: TEM image of CuO NPs

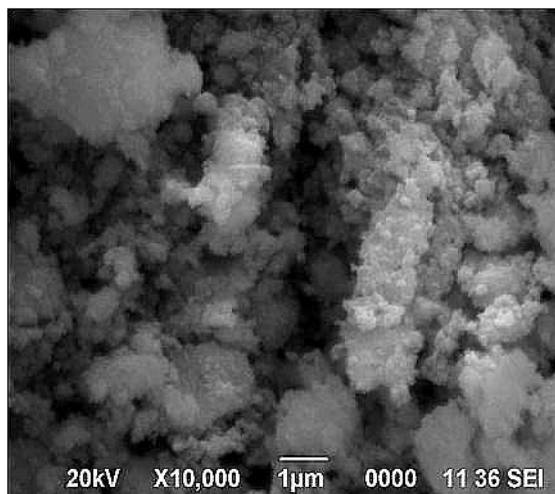


Figure 3.2: SEM image of CuO NPs

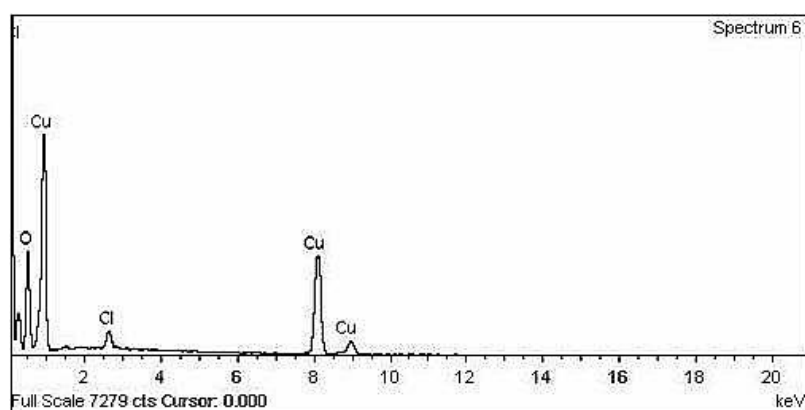


Figure 3.3: EDAX of CuO NPs

It has been observed that CuO NPs is well synthesized in rod shape. The efficiency of CuO nanorod in homo-coupling of arylboronic acid might be due to higher surface area compared to bulk counterpart. It was also investigated that bulk CuO was able to transform arylboronic acid to biphenyls with poor yield (Figure 3.4).

When bulk CuO was used more than 10 times of CuO NPs, still the biphenyls yield was poor. It is needless to mention that NPs have various unique properties that can be purposefully exploited in many spheres of practical application. Having defined the optimized reaction condition, we investigated the scope of the CuO NPs catalyzed homocoupling reaction with respect to the boronic acids. As evident from Table 3.3, most of the phenylboronic acids with a variety of substituents afforded the products in good to excellent yields under the optimum reaction conditions.

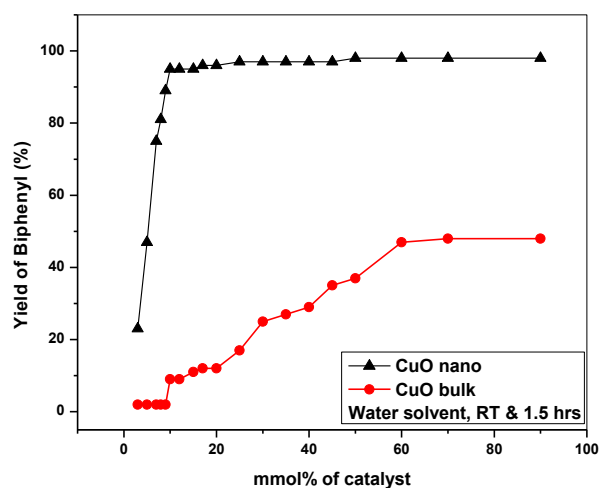
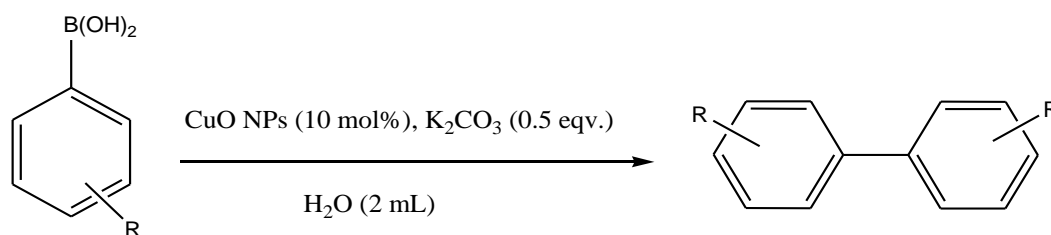


Figure 3.4: Comparison of catalytic performance of CuO NPs vs CuO bulk counterpart

Phenylboronic acids bearing electron-withdrawing fluoro, diifluoro, and formyl groups provided corresponding homo- coupling products in good to excellent yields (92–96%; Table 3.3, entries 8–12). We also investigated the homocoupling reaction of aromatic boronic acids bearing electron-donating groups. Phenylboronic acids bearing methyl, ethyl, *tert*-butyl, methoxy etc. groups gave desired products in 87–93% yields (Table 3.3, entries 2–7). It is observed that boronic acid bearing bulky group methoxypyridine undergo homocoupling reaction yielding less product. Careful inspection of the results revealed that *para*- and *meta*-substituted arylboronic acids give biaryls in good to excellent yields. Diverse results were obtained for *ortho*-substituted aryl-boronic acids which may be attributed to steric effects. As for example, the reaction of *p*-methoxyphenyl boronic acid furnished the desired product 4,4'-dimethoxybiphenyl in 90% isolated yield (Table 3.3, entry 5), demonstrating good selectivity.



Scheme 3.2: General representative scheme for the synthesis of biphenyls

Table 3.3: CuO NPs catalysed aerobic homocoupling reaction of aryl boronic acids^a

Entry	R	Products	Yield ^{b,c} (%)
1	H	Biphenyl	95
2	4-CH ₃	4,4'-Dimethylbiphenyl	85
3	3-CH ₃	3,3'-Dimethylbiphenyl	89
4	2-OCH ₃	2,2'-Dimethoxybiphenyl	86
5	4-OCH ₃	4,4'-Dimethoxybiphenyl	90
6	4-C ₂ H ₅	4,4'-Diethylbiphenyl	87
7	4- <i>tert</i> -butyl	4,4'-Di- <i>tert</i> -butylbiphenyl	91
8	4-F	4,4'-Difluorobiphenyl	94
9	3,4-difluoro	3,3',4,4'-Tetrafluorobiphenyl	93
10	4-Cl	4,4'-Dichlorobiphenyl	92
11	5-(3-methoxypyridyl)	3,3'-Dimethoxy-5,5'-bipyridine	86 ^d

^aReaction condition: Phenylboronic acid (1 mmol), CuO NPs (10 mol%), K₂CO₃ (0.5 eqv.),

^bIsolated yield, ^cAll compounds are characterized by ¹H NMR and ¹³C NMR spectroscopy. ^d2-methoxypyridine-5-boronic acid (1 mmol), CuO NPs (10 mol%), K₂CO₃ (0.5 eqv.), 60 °C, methanol solvent.

o-Methoxyphenylboronic acid produced the corresponding product 2,2'-dimethoxybiphenyl in a lower yield of 86% (Table 3.3, entry 4). With 4-ethoxypyridine boronic acid, only a trace amount of self-coupling product was formed.

3.3.2 Hot filtration test^a

The hot filtration test³⁴ is a standard method to check heterogeneity of a reaction. The reaction has been carried out at different time interval and ~71% product found after 65 mins (Figure 3.5). The CuO NPs catalyst was filtered off from the reaction mixture when ~71% of biphenyls formed. After removal of the catalyst, the reaction was monitored for an additional time upto 6 hour and no further biphenyls product was observed. Atomic absorption spectroscopy analysis of the filtrate from the reaction mixture and also of the filtrate from a stirred solution of CuO in water

under identical reaction conditions confirmed no copper leaching. These results support the heterogeneous nature of the catalyst.

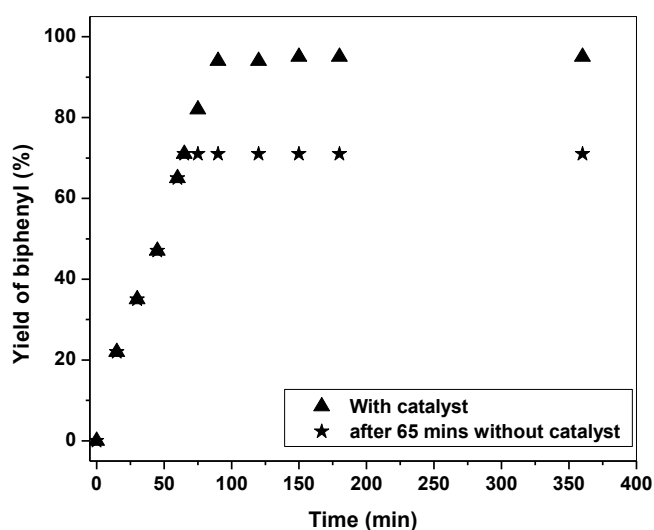


Figure 3.5: Hot filtration test^a

^aReaction conditions: phenylboronic acid (1 mmol), CuO NPs (10 mol%), water (2 mL), rt

3.3.3 Reusability of catalyst

Reusability of the CuO NPs was investigated since practical use depends on this factor. After completion of the reaction, the catalyst was recovered by filtration and washed with ethyl acetate & dry ethanol. The washed catalyst was heated at 120 °C for 2 h and activated under vacuum at rt for 2 h, which was subsequently reused and the results are presented in Figure 3.5. From this figure it is clear that the decrease in the efficiency of the catalyst resulted in a minor loss of product yield even after five times of its reuse. Comparison of the powder XRD patterns of the fresh, reused CuO up to three and five times were also studied (Figure 3.6) which clearly showed that the reused catalyst exhibited a similar powder XRD pattern. The powder XRD pattern results clearly demonstrate that no appreciable changes in the structural integrity during/after the reuse. To demonstrate the potential utility of this method for preparative purposes, the reaction was also carried out under the optimized reaction conditions on a 7.95 g scale (0.1 mol), giving 93% yield which were comparable to those obtained for a small scale reaction (reaction condition: phenylboronic acid, 200 mL water, rt, 1.5 h).

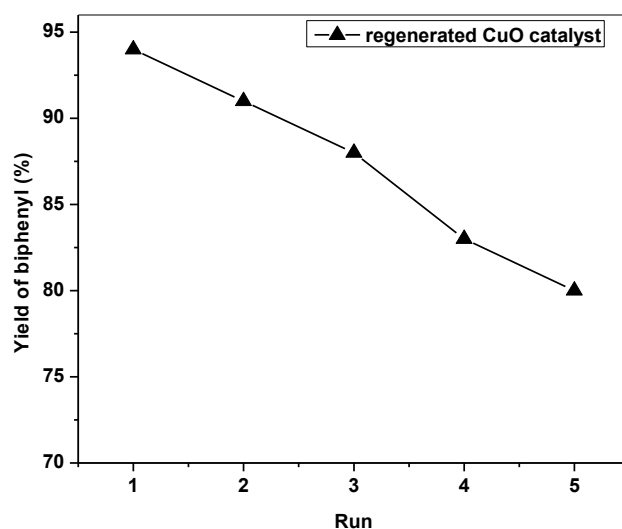


Figure 3.5: Reusability of CuO NPs catalyst

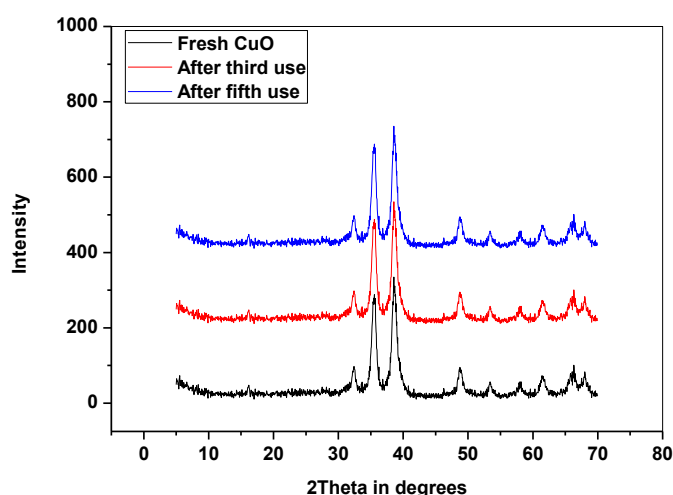
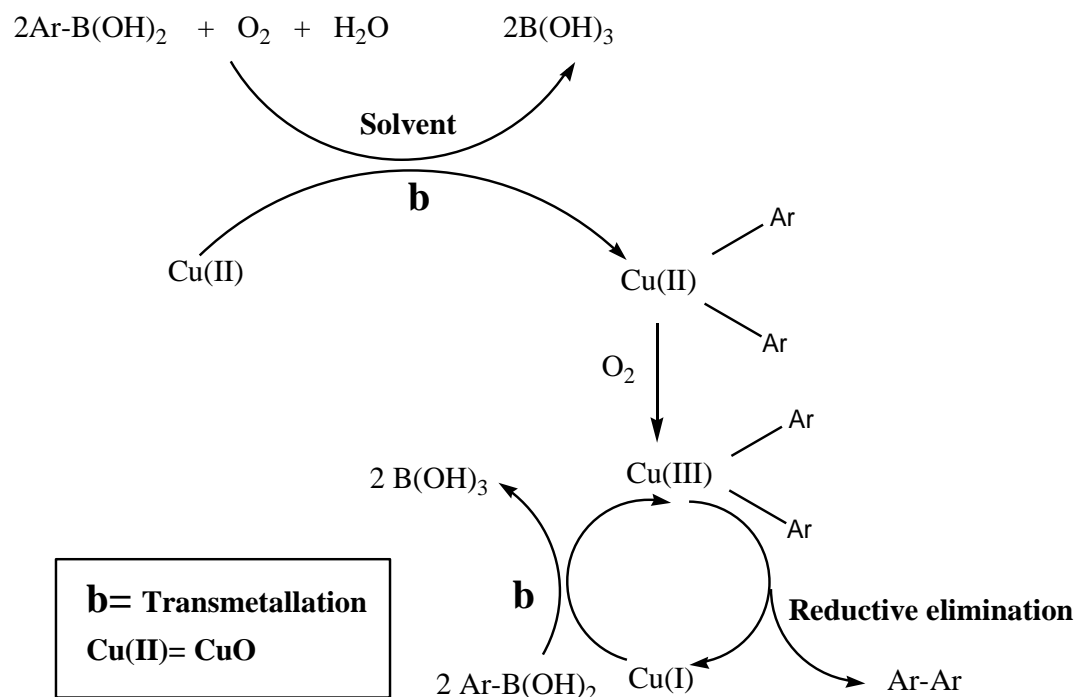


Figure 3.6: Powder XRD patterns of fresh and reused CuO NPs catalyst

The mechanism of the present reaction is not yet clear at the present stage. Hence, we have proposed a probable monometallic mechanism (Scheme 3.1) based on predicted mechanism reported by some other researchers.³⁵ The following observations may be useful to predict the mechanism: (1) Cu(II) species is catalytically active in the homocoupling reaction, (2) air is critical to the reaction, (3) the negative counterpart plays an important role and (4) solvent affects the catalyst activity profoundly. The proposed mechanism follows a Cu(I)/Cu(III) cycle. In the first step, Cu(II) may be solvated by the arylboronic acid. Double transmetallation of

Cu(II) with two molecules of arylboronic acid produces an Ar–Cu(II)–Ar, which undergoes air oxidation to yield a Cu(III) intermediate, reductive elimination of which releases the homocoupled product Ar–Ar.

Monometallic mechanism



Scheme 3.3: Plausible mechanism of homocoupling reaction

3.4. Conclusions

In conclusion, we have successfully developed a simple and efficient rod shaped CuO NPs catalyzed methodology for the homocoupling of arylboronic acids to symmetrical biaryls. The reaction proceeds in economical, cheapest and easily available solvent water under extremely mild conditions: in air, at room temperature in presence of a very mild base. The synthesized CuO NPs remain in same condition even after performing the catalytic reaction. The catalyst is efficient, easily recoverable and reusable up to another three to four times without losing its activity appreciably. This protocol is relatively inexpensive and environmentally friendly manner. The good selectivity of homocoupling over the Suzuki cross-coupling shows potential application in synthesis of biphenyls.

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36. Agro chemicals image in front page:
http://www.google.co.in/imgres?imgurl=http://www.supportbiz.com/sites/default/files/field/image/agro_0.jpg&imgrefurl=http://www.supportbiz.com/articles/market-tracker/agro-chemical-be-fastest-growing-industry-india-crisil.html&h=300&w=300&tbnid=9eaEI49XdAqLmM:&zoom=1&docid=9KQTN8vCkre_5M&hl=en&ei=W1qjVcmVEeXRmAXKnIzwDQ&tbnid=isch&ved=0CDcQMygGMAY
37. Fine chemicals industries image in front page:
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Mvno8StCM:&zoom=1&docid=Sj94JZwfcxrcHM&hl=en&ei=R1qjVZzp
HcHHmAWO_a74Cw&tbnid=isch&ved=0CD0QMygXMBc

38. Dyes image in front page:

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