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Complete List of Authors:	Taherinia, Zahra; Ilam University Faculty of Sciences Ghorbani-Choghamarani, Arash; Ilam University, Chemistry
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Cu(I)-PNF, an organic-based nanocatalyst, catalyzed C–O and C–S cross-coupling reactions

Zahra Taherinia and Arash Ghorbani-Choghamarani*

Z. Taherinia. Department of Chemistry, Faculty of Science, Ilam University, P. O. Box 69315516, Ilam, Iran. E-mail: Zahra.taheriniya@yahoo.com
Corresponding author: A. Ghorbani-Choghamarani. Department of Chemistry, Faculty of Science, Ilam University, P. O. Box 69315516, Ilam, Iran E-mail: arashghch58@yahoo.com; a.ghorbani@ilam.ac.ir; Fax: +98841 2227022; Tel: +98 841 2227022

Abstract: Peptide nanofiber has been prepared *via* a self-assembly protocol and decorated with Cu (I) to prepare a nanostructural catalyst. The catalytic activity of this prepared nano material (Cu (I)-PNF) was examined in C–O and C–S cross-coupling reactions. Compared with conventional copper-ligand catalytic systems, CuNP-PNF has unique advantages such as water solubility, high efficiency and low cost**,** which makes it a highly efficient and beneficial catalyst to reuse in cross coupling reactions.

Key words: catalyst recyclability**,** copper, peptide nanofiber, sulfide asymmetry, benzoic acid and ether

Introduction

Supported metallic nanoparticles and their catalytic applications in organic reactions and drug delivery have attracted extensive interest in recent years. Ullmann type C-S and C-O bond formation reactions are very important and powerful tools for numerous applications in the pharmaceutical, agrochemical and polymer industries. Due to the high costs associated with palladium-based catalyst systems, the past decade has seen the development of a multitude of copper catalysts for heteroatom bond formations. The effectiveness of the previously reported catalytic systems for the synthesis of C-heteroatom bonds required harsh reaction conditions, stoichiometric amounts of promoters, use of strong bases, and bipyridine or phosphine-type ligands [1-3]. Hence, it is necessary to find an efficient procedure to overcome these drawbacks. A shift toward copper nanoparticles has been apparent in the past decade because they offer advantages specific to both heterogeneous and homogeneous catalysts and for this reason they are sometimes called "semi-heterogeneous" catalysts [4]. Metal nanoparticles easily agglomerate and oxidize due to high surface energy in aqueous solutions, hence, immobilized on a support that acts as a stabilizing agent. Recently, polymeric and composite materials [5], boehmite[6], zeolites [7], dendrimers [8], MCM-41[9], activated carbon[10], carbon nanotube[11] and nanofiber [12] have been used as supports because the support acts as a stabilizing agent to prevent aggregation of the nanoparticles. Among these supports, nanofibers ranging from micron to nanometer scales have created interest due to their unique high surface areas to volume ratio, film thinness, lighter weight and super

thermal stability, and they could be easily recycled due to their one-dimensional structure. Nanofibers can be generated by numerous techniques such as drawing [13], template synthesis [14], self-assembly [15], electro spinning [16]. Self-assembly is the most popular fabrication strategy. Self-assembly is a process in which individual molecules organize and arrange themselves into patterns or structures due to structural complementarities with hydrogen bonding, electrostatic interactions, hydrophobic affinity, etc. Factors such as concentration of peptide molecules, pH, solvent polarity, sonication, ionic strength, interaction with anions such as phosphate are also expected to affect the self-assembly. Self-assembling peptides are relatively scarce and particularly interesting due to wide application in tissue engineering [17], drug delivery [18] and use as platforms for presenting antigen epitopes[19]. However, to achieve an efficient simple fabrication, we demonstrate the self-assembly of a peptide with arginine as the building block. After

the peptides self-assemble into nanofibers copper nanoparticles were immobilized on the surface of this nanostructural compound and we studied the catalytic ability for C-O, and C-S coupling reactions. The formation of a bond between sp^2-carbon and sulfur atoms has received less attention, despite the fact that sulfides have wide application as potent drugs for HIV [20], Alzheimer [21], and Parkinsons diseases [22] and are important intermediates in organic synthesis [23]. These sulfides were traditionally prepared via the reduction of sulfones or sulfoxides involves strong reducing agents, such as DIBAL-H or $LiAlH_4$ [24-27] and the cross-coupling reactions of aryl halides with thiols in the presence of copper [28-29], palladium [30], nickel [31], cobalt [32], iron [33], and indium [34] catalysts. However, arenethiols are susceptible to oxidative homo coupling to give disulfides as by-products. Decarboxylation of carboxylic acids by loss of carbon dioxide (CO_2) has recently emerged as efficient and new methods for the construction of C–C and C-Se bonds [35] but the formation of carbon-sulfur bonds was only very recently reported via the copper-catalyzed, 2-substituted arene carboxylic acid and a thiol or disulfide in the presence of arenecarboxylic acid containing an electron-withdrawing group [36] (Scheme 1). It is particularly noteworthy that for the first time we have demonstrated the preparation of aryl sulfides from direct decarboxylative C-S coupling of aryl halides and aryl carboxylic acids (without the need of an electron-withdrawing group on the arenecarboxylic acid) in the presence of S_8 as a sulfur source and an efficient catalyst (Scheme 1). In addition this catalyst exhibits high catalytic activity in C–O bond forming reactions.

Scheme 1

Results and Discussion

In our newly published work we investigate the activity of peptide nanofiber decorated with copper as an effective catalyst for the decarboxylative *N*-arylation of substituted benzoic acids as well as synthesis of 5-substituted *1H*-tetrazoles (Figure1) [37]. Peptide nanofiber decorated with Cu features led us to further study the scope of peptide nanofibers for the catalysis of C-O, C-S cross-coupling reactions.

Catalytic studies

After characterization of Cu (I)-PNF, the catalytic activity of this nanostructural compound has been investigated for C-hetroatom coupling reactions (including C-O and C-S bond formation). Initially, we examined coupling reactions

of 4-iodoanisole with 4-bromobenzoic acid and S_8 in the presence of catalytic amounts of Cu(I)-PNF, and various parameters were optimized to achieve the best coupling conditions Table 1. It was found that the base and solvent significantly affected the yield of the desired product. Among organic and inorganic bases, the most favorable one was found to be KOH. Also among tested solvents, DMSO and DMF both gave the best yields compared with other solvents (Chart 1, entries 3, 5). The amount of Cu (I)-PNF was optimized to reveal that the best results were obtained in the presence of 1.28 $g.L^{-1}$ of catalyst. The results also show that this coupling reaction is strongly dependent on reaction temperature. When the reaction was conducted at 100 °C, the observed yield was very low (table1, entries 14), however, the ideal temperature for coupling reaction was found to be 130 °C. Also, other sulfur sources such as thiourea and thioacetamide were examined for the model reaction but their observed yields were very low. It should be mentioned when the reaction conducted in the presence of CuCl in the similar conditions (Table1, entry 19), the yields observed were low. We proposed that this reaction occurred via reaction iodoobenzene with S_8 for the synthesis of symmetrical aryl sulfides, because decarboxylation happens very slowly. Eventually the best results were obtained with 4-iodoanisole (1 mmol), 4-bromobenzoic acid (1.2 mmol), S_8 (1.5 mmol) and KOH (4 mmol) in the presence catalytic amounts of Cu (I) immobilized on woven nanofiber (200 µl) in DMSO as solvent at 130 °C (Table 1). The generality of this nanoparticles Cu (I)-PNF was investigated on the substrate scope for the C-S cross-coupling reaction under the optimized reaction conditions (Chart 1,1a-3g).

Scheme 2

Table 1

Experimental results show that halide derivatives with different functional groups, such as OCH_3, NO_2, Cl, Br and I provide good to excellent yields of the corresponding sulfides. Meanwhile, in some cases the coupling reaction of aryl halides containing electron withdrawing substituent's reacted in shorter reaction time than aryl halides with electron-donating groups.

Scheme 3

Table 2

Chart 1(3a-3g)

The proposed mechanism for the C-S cross-coupling reaction based on previous reports is depicted in Scheme 4 [38]. Initially S_8 reacts with KOH to give potassium disulfide. Then the peptide nanofiber decorated with Cu

nanoparticles reacts with potassium disulfide to give copper disulfide, which adds to benzoic acid *via* an oxidative addition reaction to produce intermediate **1**. This subsequently forms intermediate **2**. Aryl halide reacts with intermediate **2** by oxidative addition to generate **3**, which can undergo reductive elimination to afford diaryl sulfide.

Scheme 4.

The reactivity of *Cu (I) supported on woven peptide nanofiber* was also examined for the cross-coupling reaction between aryl halides with 4-bromophenol and 4-chlorophenol. In order to optimize reaction conditions, the coupling reaction between iodobenzene and 4-chlorophenol was selected as the model reaction and various parameters were optimized (Table 3). All the reactions were carried out under standard conditions and manipulated without any special precaution. According to results in Table 3, it was found that among organic and inorganic bases, KOH was found to be the most effective base for this reaction. The effect of solvents was also investigated and it was observed that the desired product was obtained in DMSO and the coupling reaction in other solvents (such as DMF, PEG and H_2O) didn't give satisfactory result. Basis on these results, the optimal conditions involved the following parameters: iodobenzene (1 mmol), 4-chlorophenol (1 mmol), Cu (I)-PNF (200µl), KOH (1.5 mmol), DMSO (2 mL) and 130 °C as reaction temperature. Under optimized reaction conditions, a series of structurally various aryl halides was subjected to the reaction with 4-bromophenol and 4-chlorophenol. The results are summarized in Chart 2(4a-6i), the results showed that the aryl halide derivatives with different functional groups, such as CH_3, OCH_3 and NO_2, provide desired products in good to excellent yields (Table 4).

Scheme 5

Table 3

Scheme 6

Table 4

The proposed mechanism for the C-O cross-coupling reaction on the basis of previous reports [39] is illustrated in Scheme 7. Initially aryl halide reacts with Cu by oxidative addition to form intermediate (*a*), then the intermediate (*a*) reacts with 4-chlorophenol in the presence of the base KOH to provide intermediate **(*b*)**, then intermediate **(*b*)** *via* reductive elimination afford ether and releases the copper nanoparticle.

Scheme 7

Catalyst recyclability

The reusability of a catalyst is one of the most important aspects in industrial point of view. The recyclability of described catalyst (Cu (I)-PNF) was examined by the cross-coupling reaction of benzoic acid with iodobenzene as a model reaction. Upon completion of the reaction, the mixture was cooled to room temperature. 20 mL of ethyl acetate was added to the reaction mixture, which led to the precipitation of Cu (I)-PNF. The resulting precipitate was washed twice with ethyl acetate (2 x 10 mL), dried and applied for the next run. It was found that Cu (I)-PNF could be reused at least four times without a significant loss of its catalytic activity (Fig 2). Also hot filtration technique was done for the synthesis of diphenyl sulfide when the reaction had preceded to nearly50% completion, by adding ethyl acetate to the reaction mixture, this led to the precipitation of Cu (I)-PNF. The resulting precipitate was washed twice with ethyl acetate (2 x 10 mL), and then filtered. The filtrate was evaporated under vacuum; DMSO (2 mL) was added and allowed the filtrate to react further. We found that no further reaction occurred after the separation of catalyst; this means that the Cu (I) catalyst remains on the support at elevated temperatures during the reaction.

Figure 2

In summary, a novel copper-based peptide nanofiber catalyst was successfully prepared by a simple self-assembly method and used as a catalyst with excellent activity for C–O and C–S bond formation. In this research for the first time we demonstrate application of peptide nanofiber decorated with inexpensive copper (I) instead of palladium and toxic phosphane-containing ligands for C–S bond formation by decarboxylative C-S cross-couplings

Experimental

Chemicals and solvents used in this work were obtained from Sigma-Aldrich, Fluka or Merck chemical companies and used without further purification.

Preparation of peptide nanofiber (PNF)

Peptide nanofiber has been prepared by our newly published procedure [10].

Synthesis of Cu nanoparticle supported on the peptide nanofiber (CuNP-PNF)

For the synthesis of CuNP-PNF catalyst, 30.14 mg of peptide was dissolved in 0.2 mL of doubly distilled water and 0.8 mL phosphate buffer solution (pH 8) and the solution was sonicated for a few minutes, then stirred at 80°C overnight. In the next step CuCl (2.2 mg, 0.02 mmol) was added to the reaction mixture and heated to 80°C for 12 h. Upon stirring, solution suspension of Cu nanoparticle supported on the peptide nanofiber was formed [37].

General procedure for C-S cross-coupling reaction

S_8 (1.5 mmol), benzoic acid (1.2 mmol), aryl halide (1 mmol), 200µL of the solution containing Cu nanoparticle decorated on nanofibers and KOH (4 mmol) were stirred at 130 °C in DMSO (2 mL). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture extracted with ethyl acetate (3 x 20 mL). The organic layer was washed twice with water and dried with Na_2SO_4. Finally, evaporation of the solvent then purification by column chromatography on silica gel (*n*-hexane/EtOAc) achieves corresponding sulfide.

General procedure for C-O cross-coupling reaction

Phenol (1 mmol), aryl halid (1 mmol), Cu nanoparticle supported on the peptide nanofiber (Cu (I)-PNF), (200 µl) and KOH (1.5 mmol) were stirred at 130 °C in DMSO (2 mL). The progress of the reaction was monitored by TLC using ethyl acetate and n-hexane as eluent. After completion, the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The organic extract was washed twice with water and dried with Na_2SO_4 then evaporated. The products purified by thin layer chromatography.

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Captions

Scheme 1. Approaches to C–S bond formation

Scheme 2. Preparation of C–S bond formation

Scheme 3. Synthesis of C–S bond formation

Scheme 4. Proposed mechanism for the synthesis of unsymmetrical sulfides

Scheme 5. Preparation of C–O bond formation

Scheme 6. Synthesis of C–O bond formation

Scheme 7. Proposed mechanism for C-O cross-coupling

Fig 1. SEM images of (a,b and c) immobilised Cu nanoparticles on the surface of the woven nanofibers

Fig. 2 Catalyst recycling studies

Table 1 Optimization of the reaction conditions for the C-S bond forming

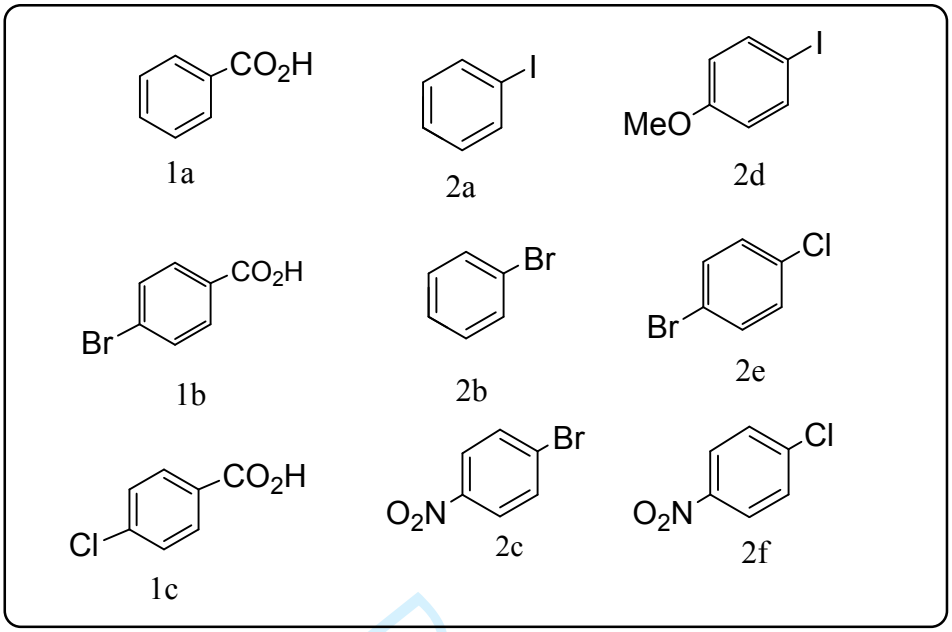
Table 2 Synthesis of unsymmetrical sulfides *via* reaction of benzoicacid and aryl halides/S_8 catalyzed by peptide nanofibers decorated with Cu nanoparticles (CuNP-PNF) in DMSO.

Table 3. Optimization of the reaction conditions for the C-O cross-coupling between iodobenzene and 4-chlorophenol.

Table 4. Cu(I)-PNF catalyzed C-O cross-coupling of Substituted phenols with aryl halides.

Chart 1(1a-3g). A series of several unsymmetrical sulfides

Chart 2(4a-6i). A series of several unsymmetrical ethers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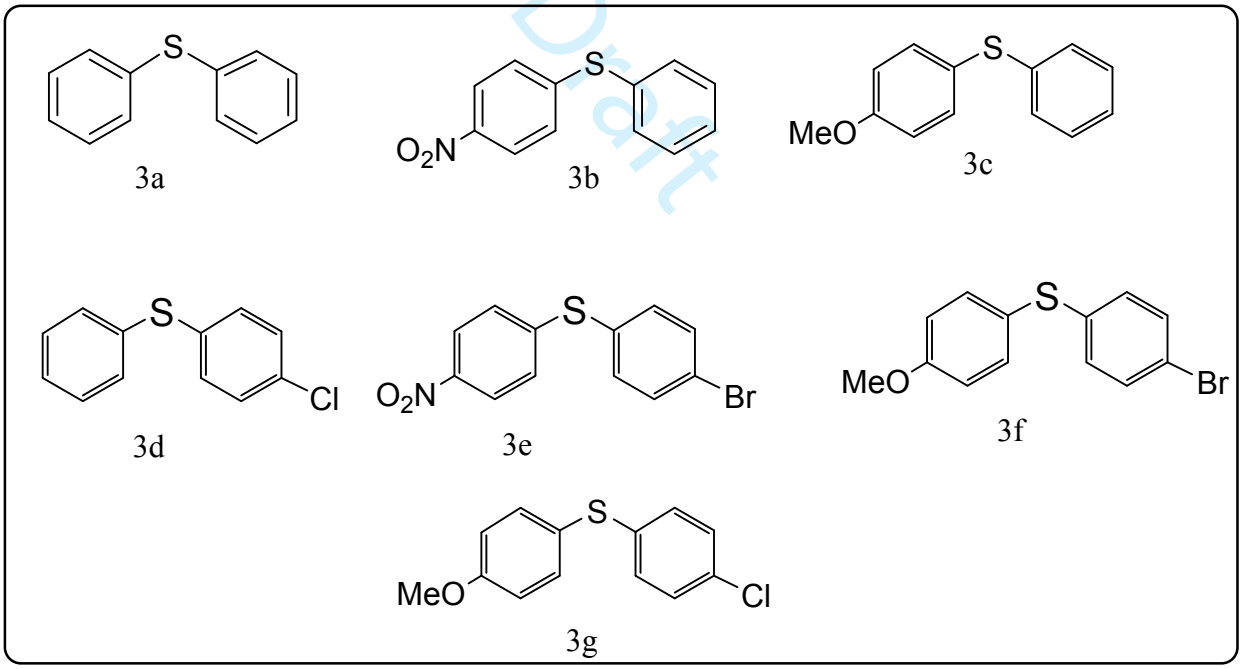
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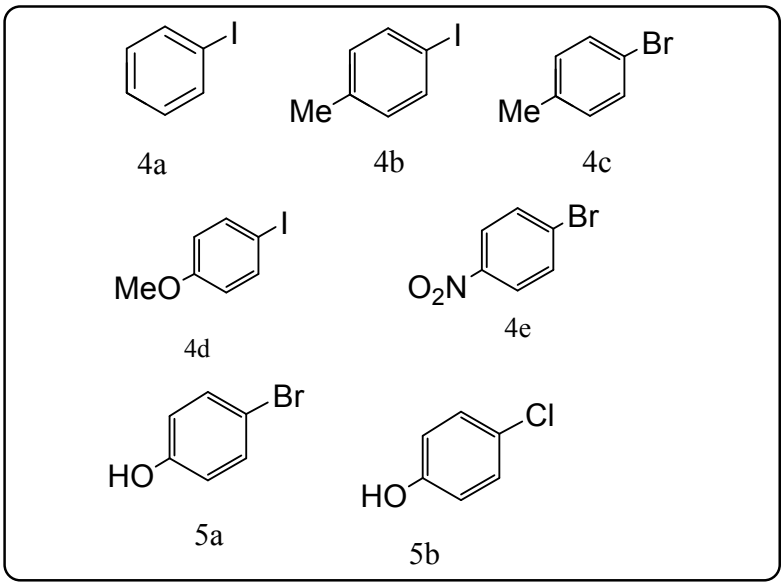
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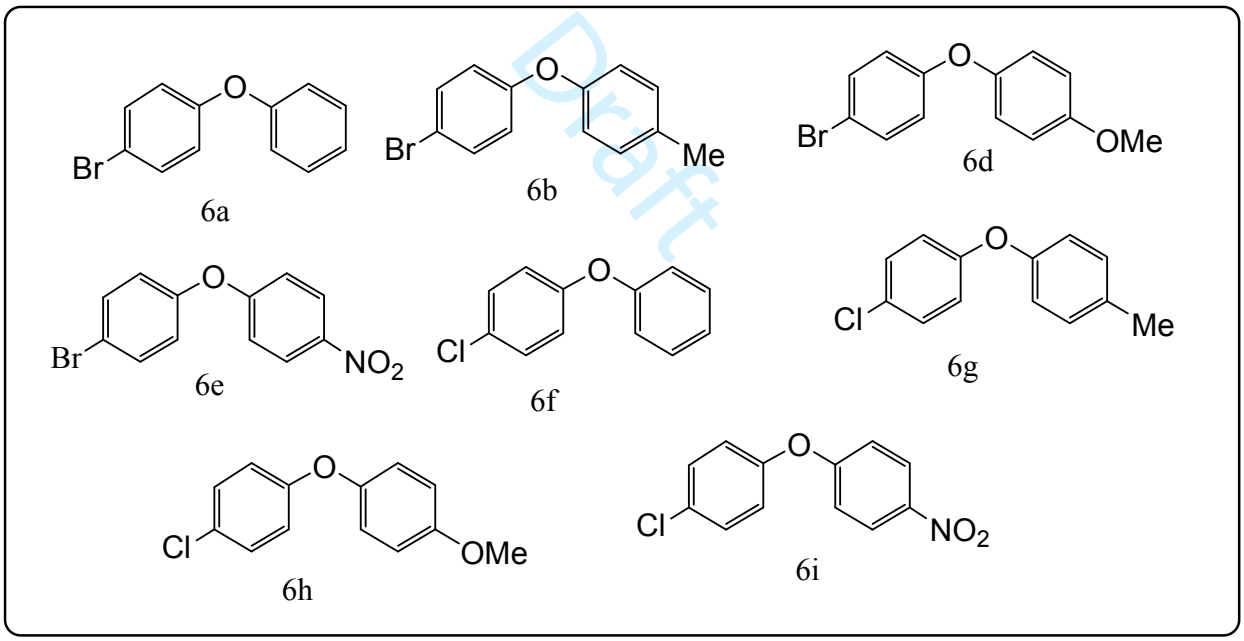
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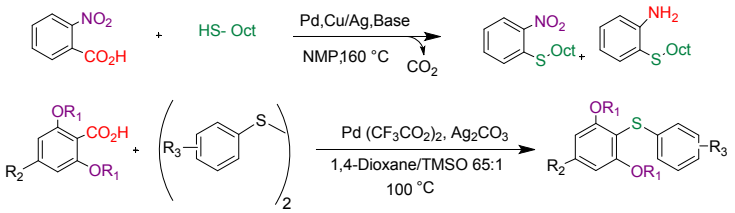
Previous works



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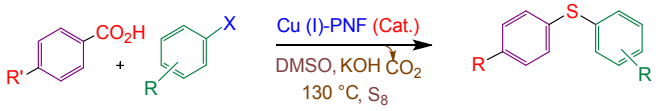
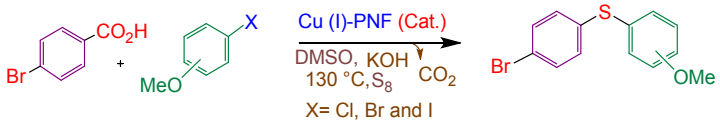
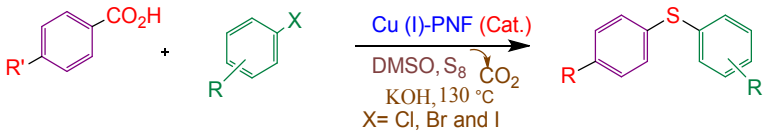


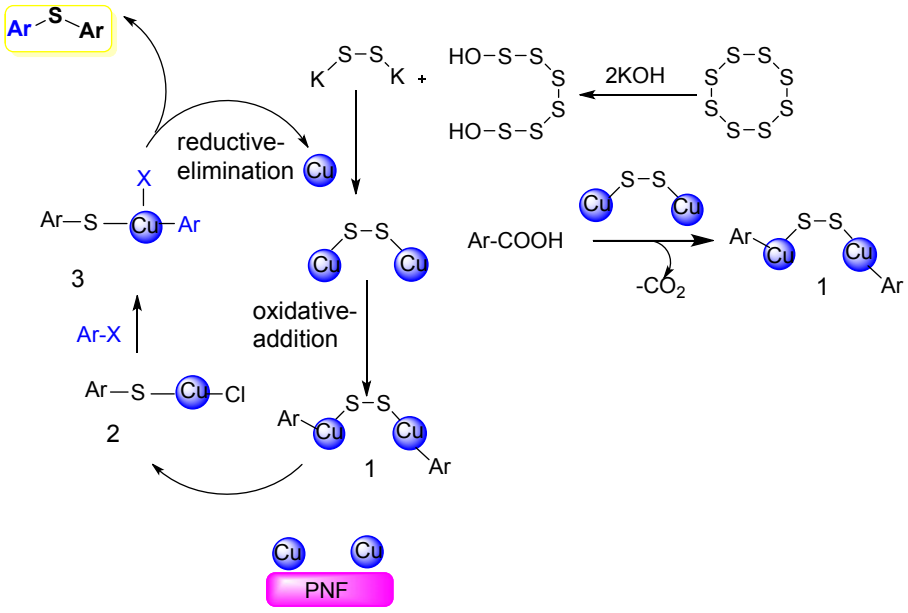
Scheme 1



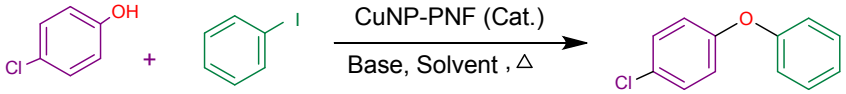
Scheme 2



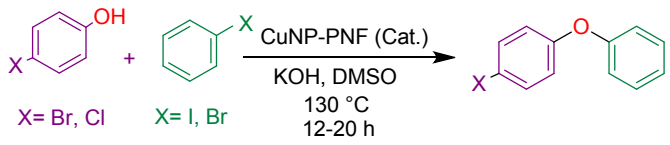
Scheme 3



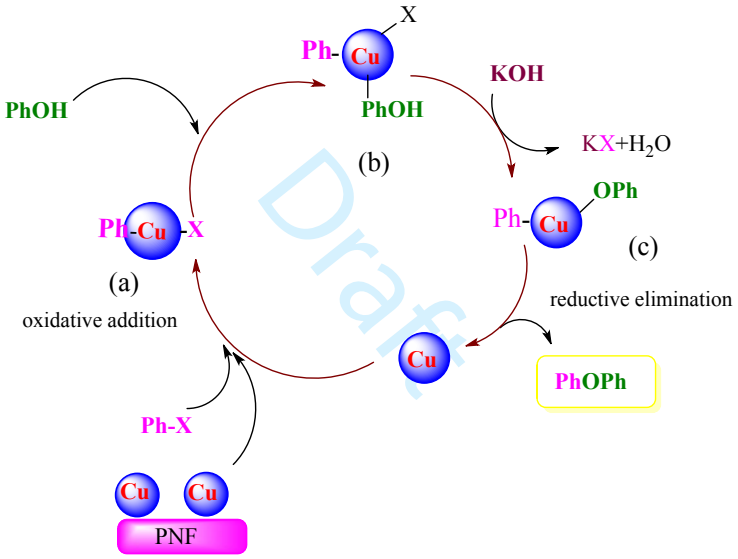
Scheme 4



Scheme 5



Scheme 6



Scheme 7

Table 1

Entry [a]	S source	Cat. (µl)	Solvent	Temp. (ºC)	Base	Base (mmol)	Yield [b]
1	thiourea	200	DMSO	130	KOH	4	N.R
2	thioacetamide	200	DMSO	130	KOH	4	30
3	S_8	200	DMSO	130	KOH	4	82
4	S_8	200	PEG	130	KOH	4	N.R
5	S_8	200	DMF	130	KOH	4	43
6	S_8	200	H_2O	100	KOH	4	N.R
7	S_8	200	EtOH	80	KOH	4	N.R
8	S_8	200	CH_3CN	80	KOH	4	N.R
9	S_8	200	DMSO	130	Et_3N	4	N.R
10	S_8	200	DMSO	130	KF	4	N.R
11	S_8	200	DMSO	130	NaOH	4	63
12	S_8	200	DMSO	130	K_2CO_3	4	N.R
13	S_8	200	DMSO	130	Na_2CO_3	4	N.R
14	S_8	100	DMSO	130	KOH	4	28
15	S_8	200	DMSO	100	KOH	4	43
16	S_8	200	DMSO	130	-	-	N.R
17	S_8	200	DMSO	130	KOH	1.5	trace
18	S_8	200	DMSO	130	KOH	2.5	37
[C]19	S_8	200	DMSO	130	KOH	4	43

[a]Reaction conditions:4-iodoanisole (1 mmol), 4-bromobenzoic acid (1.2 mmol), base, Cu (I)-PNF (µl), S_8 (1.5 mmol) and solvent (2 mL). [b]Isolated yield. [C] in the presence of CuCl

Table 2

Entry[a]	Acid	Ar-X	product	Time (h)	m.p	Yield [b]
1	1a	2a	3a	11	oil[40]	92
2	1a	2b	3a	13	oil[40]	72
3	1a	2c	3b	8	54-56[41]	75
4	1a	2d	3c	20	oik[42]	85
5	1a	2e	3d	18	oil[43]	82
6	1b	2c	3e	11	92-95[44]	65
7	1b	2d	3f	24	55-57[45]	82
8	1b	2f	3e	14	92-95[44]	61
9	1c	2d	3f	24	63-65[46]	90
10	1c	2c	3g	8	80-83[44]	80

[a]Reaction conditions:4-iodoanisole (1 mmol), 4-bromobenzoic acid (1.2 mmol), base (4 mmol), Cu (I)-PNF (200µl), S_8 (1.5 mmol) and solvent (2 mL).
[b]Isolated yield.

Table 3

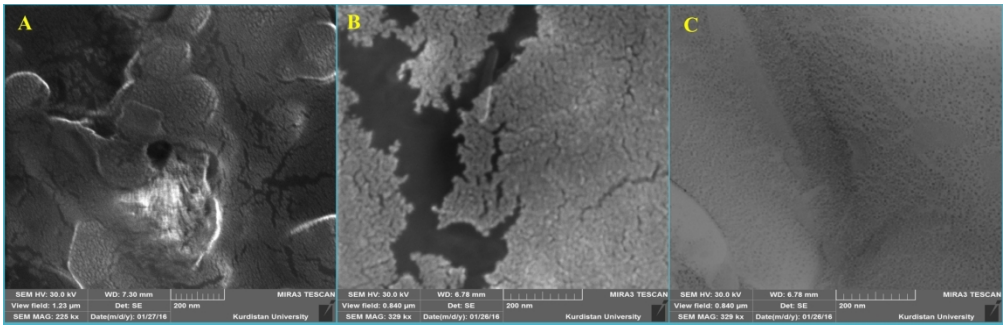
Entry [a]	Cat (µl)	solvent	Temp. (ºC)	base	mmol of base	Yield [b] (%)
1	200	DMSO	130	KOH	1.5mmol	78
2	200	DMF	130	KOH	1.5mmol	N.R
3	200	PEG	130	KOH	1.5mmol	N.R
4	200	H_2O	130	KOH	1.5mmol	N.R
5	200	DMSO	130	Et_3N	1.5mmol	N.R
6	200	DMSO	130	KF	1.5mmol	N.R
7	200	DMSO	130	K_2CO_3	1.5mmol	N.R
8	200	DMSO	130	Na_2CO_3	1.5mmol	N.R
9	200	DMSO	80	KOH	1.5mmol	trace
10	200	DMSO	100	KOH	1.5mmol	43
11	100	DMSO	130	KOH	1.5mmol	17
12	200	DMSO	130	-	-	N.R
13	200	DMSO	130	KOH	3mmol	55

[a]Reaction conditions: Iodobenzene (1 mmol), 4-chlorophenol (1 mmol), base, solvent (2 mL) and Cu(I)- PNF (µl). [b]Isolated yield.

Table 4

Entry [a]	Ar-X	Phenol	Product	m.p	Yield [b] (%)
1	4a	5a	6a	55-57[47]	85
2	4b	5a	6b	65-68[48]	75
3	4c	5a	6b	65-68[48]	70
4	4d	5a	6d	81-83[48]	80
[c]5	4e	5a	6e	90-94[49]	82
6	4a	5b	6f	oil[50]	78
7	4b	5b	6g	53-56[51]	65
8	4c	5b	6g	53-56[51]	53
9	4d	5b	6h	52-54[52]	70
[d]10	4e	5b	6i	70-73[51]	75

[a]Reaction conditions: iodobenzene (1 mmol), phenol (1mmol), KOH (1.5mmol), Cu(I)-PNF (200µl) and solvent (2 mL). [b]Isolated yield. [c and d] time (8h)



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