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Green synthetic method of *N*-arylamides using recyclable cheap metal catalyst

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ABSTRACT

Magnetically separable and reusable Fe/Cu oxide (Fe_3O_4-Cu_2O) nanoparticles were employed as an efficient catalyst for the arylation of benzamide, which was carried out with a range of both arylboronic acid and benzamide to afford *N*-arylamide in good to excellent yield.

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N-Arylamides are important subunits found in natural products that have applications in material sciences, pharmaceuticals, and as biologically active inhibitors[1]. In addition to the traditional synthetic reactions from carboxylic acid derivatives and amines [2], modern C—N coupling reactions also appear in the literature.. While many significant Pd-catalysed C—N cross-coupling reactions have been developed in recent years[3], the use of expensive palladium and elaborate phosphorylated ligands limit their applications in large-scale production. Therefore, the copper catalytic system has received extensive attention. Mukkamala et al[4]. reported a C—N bond-forming reaction between phenylboronic acid and benzamide catalysed by copper(I) iodide. But the reaction needs to be carried out under oxygen conditions, and the catalyst cannot be recovered. Constructing C—N bonds with iodobenzene and amine compounds at the same time has also been a focus of researchers. Ribas et al.[5] reported a C—N bond-forming reaction between iodobenzene and benzamide catalysed by copper(I) iodide. Islam et al.[6] successively reported that copper catalyst was prepared from chloromethyl polystyrene and nanoparticle-graphene-based composite materials, used as catalyst for *N*-arylation and *O*-arylation. Punniyamurthy et al.[7] used CuO to catalyze the coupling of phenylboronic acid and benzamide with a yield of 15%. However, transition metals as catalysts face problems that are difficult to separate and recover.

Supported-magnetic catalysts have received great attention in recent years and are an integral part of catalysis science and technology[8]. A magnetic catalyst can exhibit improved performance and be conveniently orientated, separated from the catalytic process. Usually, metals and metal oxides can be loaded on Fe_3O_4 nanoparticles (NPs) for easy separation by magnetism. Wei et al. [9] reported building a C—N bond catalyzed by recyclable, low-cost and environmentally benign magnetic nanoparticles of ferrite complex oxides. Ramon et al.[10] described copper impregnated in a magnetite catalyst as an efficient and green catalyst for the selective multicomponent reaction of terminal alkynes, aldehydes and secondary amines. Phukan et al.[11] reported Cu-doped $CoFe_2O_4$ nanoparticles as magnetically recoverable catalyst for C—N cross-coupling reaction. In addition, Gawande[12], Sharma[13], Shelke[14] and others[15] reported the application of copper nano-magnetic catalyst for the C—N bond formation. Although much progress has been achieved, it is still necessary to develop a green and efficient method for synthesizing *N*-arylamides by the coupling reaction. In this paper, we report a *N*-arylation of benzamides with arylboronic acids using Fe_3O_4-Cu_2O nanoparticles as a catalyst, which can be easily recovered.

Fe_3O_4-Cu_2O NPs were prepared according to Guo et al.[16]. The amount of copper supported on the Fe_3O_4, measured by inductively coupled plasma mass spectrometry (ICP-MS) analysis, was 0.64 g of Cu per g of catalyst (10.1 $mmol.g^{-1}$). The crystalline nature and composition of the as-synthesized products were characterized by XRD, as shown in Fig 1. Six

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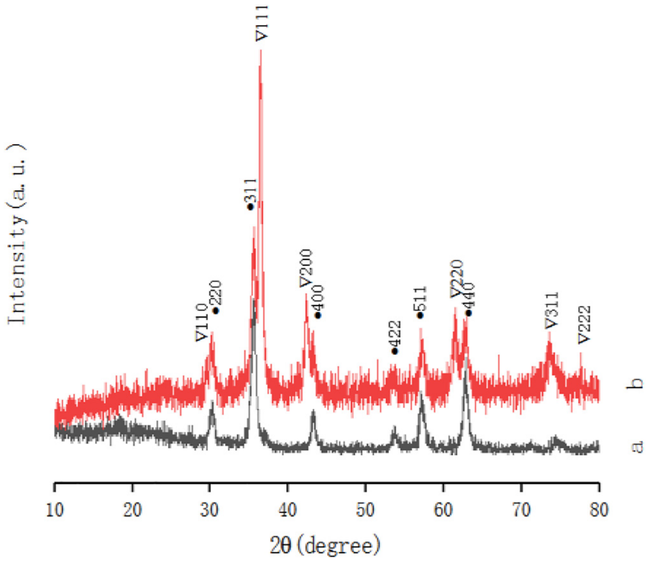


Fig 1. XRD patterns of (a) Fe_3O_4 NPs and (b) Fe_3O_4–Cu_2O NPs..

major reflections located at approximately 30.1, 35.4, 43.1, 53.3, 56.9 and 62.5 can be respectively assigned to the diffraction of Fe_3O_4 NPs with a cubic phase from the (220), (311), (400), (422), (511) and (440) planes (JCPDS 19–0629) (Fig 1 line a), indicating the crystalline cubic phase of the catalyst. For the XRD pattern of the Fe_3O_4-Cu_2O composite (Fig 1, line b), the main peaks are similar to those of the native Fe_3O_4 particles, which reveals that the crystal structure of the Fe_3O_4 is well-maintained after the loading by Cu_2O during the reaction process. Compared to pure Fe_3O_4, new diffraction peaks located at approximately 29.6, 36.4, 42.3, 61.3, 73.5 and 77.3 can be assigned to the diffraction of Cu_2O rhombic dodecahedral crystals in the cubic phase from the (110), (111), (200), (220), (311) and (222) planes respectively (JCPDS 05–0667).

The morphology of the samples was determined using SEM images (Fig 2). It can be seen that the Fe_3O_4 NPs are spherical particles with a uniform size and a diameter between 18 and 23 nm. From Fig 3, the Cu_2O is supported on the surface of the Fe_3O_4. The Cu_2O is visible as spherical particles with a particle size of approximately 580 nm.

After we obtained the Fe_3O_4-Cu_2O NPs, we started our investigation by performing an optimization of the solvents, bases and ligands used for the coupling of benzamide and phenylboronic acid, which were used as model substrates. The results for the different reaction conditions are summarized in Table1. In an initial trial, we examined different bases in the absence of ligands. Of the several bases chosen, KOH had the best effect for this transformation, leading to a 42% yield of 3a (Table 1, entry 1). Other bases such as K_2CO_3, Na_2CO_3 and Cs_2CO_3 had poorer performance, affording lower yields of 10, 24 and 36%, respectively (Table 1, entries 2–4). Then, we tested four ligands, triphenylphosphine (L1), N,N'-dimethylethylenedi-amine) (L2), 4-dimethylaminopyridine (L3) and 1,2-bis(diphenyl-phosphino)ethane (L4). Among them, L3 was the most effective, and the yield of 3a was 59% (Table 1, entry 7), while those for the other three ligands were 39%, 46% and 33%, respectively (Table 1, entries 5, 6 and 8). Next, the reaction was carried out using different solvents, including DMF, toluene, CH_3OH and CH_3CN, to examine the solvent effect. We found that none of these four solvents was as good as DMSO, providing 3a at 49%, 54%, 35% and 28% yields, respectively (Table 1, entries 9–12). We then optimized the amounts of base and catalyst. When the amount of the base increased to 1.5 mmol, the yield of 3a increased to 69% (Table 1, entry 13). While the use of 2 mmol of base led to a yield of 80% (Table 1, entry 14). The further addition of KOH to 2.5 mmol did not further improve the yield (Table 1, entry 15). Notably, the amount of base is an important parameter in this reaction system. Regarding the amount of catalyst, it was found that the yield decreased when 25 mol% of the catalyst was used (Table 1, entry 16). When the catalyst was increased to 35 mol%, the yield did not change and remained at 80% (Table 1, entry 17).

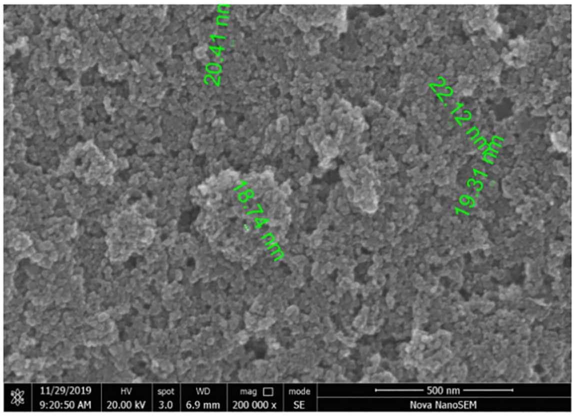


Fig 2. SEM image of Fe_3O_4 NPs.

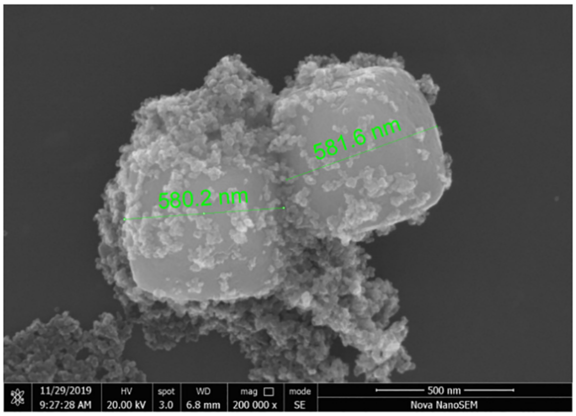
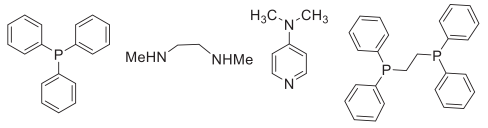


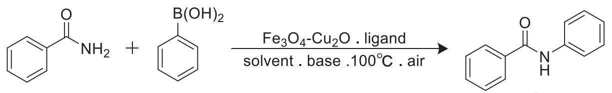
Fig. 3. SEM image of Fe_3O_4–Cu_2O NPs.

After optimizing the reaction conditions, we explored the scope of the substrates for this Cu_2O-catalysed coupling of benzamides and arylboronic acids (Table 2). Under optimal conditions, most substrates were obtained in excellent yields. First, a series of arylboronic acids were employed to react with benzamide (Table 2, entries 1–6). As shown in this table, the yields from arylboronic acids with an electron-withdrawing group on the benzene ring were high, such as those achieved with 4-chloro (85%), 3-chloro (82%) and 4-fluoro (89%) (Table 2, entries 2–4). For phenylboronic acids with an electron-donating group, such as 4-methyl or 4-methoxy groups (Table 2, entries 5 and 6), relatively low yields were obtained 79 and 78%, respectively.The results indicate that electron-withdrawing groups on the aryl ring are more favourable than electron-donating groups. Then, benzamide with various substituents (Cl, F, NO_2 and Me) was used for the present coupling reaction. Strong electron-withdrawing groups, including NO_2 and F, afforded a better yield (85 and 89% respectively), followed by the chlorinated product (ca. 70%). The weaker electron-donating methyl group had a somewhat lower yield of 65% (Table 2, entries 7–11). Further

Table 1
Optimization of reaction conditions [a]



L1 L2 L3 L4



1a 2a 3a

Entry	Ligand	Solvent	Base	Yield [b](%)
1	–	DMSO	KOH	42
2	–	DMSO	K_2CO_3	10
3	–	DMSO	Na_2CO_3	24
4	–	DMSO	Cs_2CO_3	36
5	L1	DMSO	KOH	39
6	L2	DMSO	KOH	46
7	L3	DMSO	KOH	59
8	L4	DMSO	KOH	33
9	L3	DMF	KOH	49
10	L3	Toluene	KOH	54
11	L3	CH_3OH	KOH	35
12	L3	CH_3CN	KOH	28
13[c]	L3	DMSO	KOH	69
14[d]	L3	DMSO	KOH	80
15[e]	L3	DMSO	KOH	80
16[f]	L3	DMSO	KOH	78
17 [g]	L3	DMSO	KOH	80

[a] Reaction conditions: phenylboronic acid (1 mmol), benzamide (0.5 mmol), catalyst (30 mol%), ligand (20 mol%), solvent (2 mL), base (1 mmol), 100℃, 2 h, air. [b] Isolated yield. [c] 1.5 mmol of KOH. [d] 2 mmol of KOH. [e] 2.5 mmol of KOH. [f] 25 mol% of catalyst. [g] 35 mol% of catalyst.

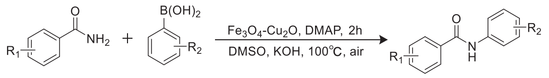
illustrative examples of the coupling reactions of benzamides and arylboronic acids with various substituents on the phenyl ring of both substrates are outlined below (Table 2, entries 12–18). Generally, a variety of combinations were compatible, and the C—N coupling proceeded with a range of amides and arylboronic acids with good to excellent yields (78–93%). In particular, upon the treatment of an aliphatic amide with phenylboronic acid, the corresponding coupling product was obtained with a moderate yield of 68% (Table 2, entry 19).

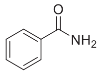
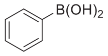
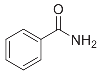
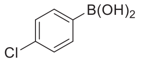
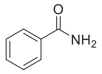
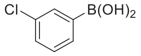
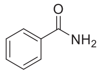
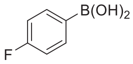
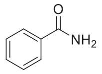
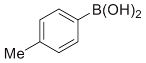
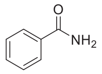
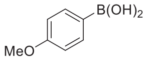
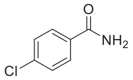
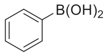
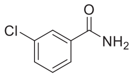
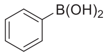
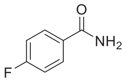
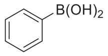
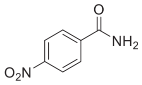
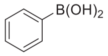
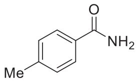
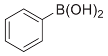
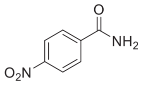
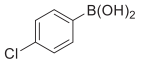
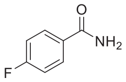
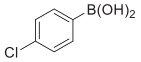
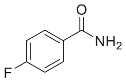
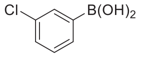
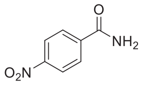
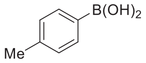
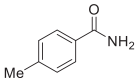
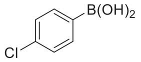
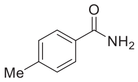
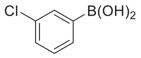
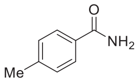
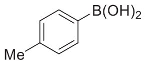
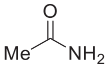
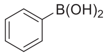
To evaluate the reusability the of Fe_3O_4-Cu_2O NPs, six continuous runs were performed using benzamide and phenylboronic acid under optimal conditions. After the end of each reaction, the reaction mixture was filtered, and the catalyst was reused in the next batch. We found that the catalyst can be reused up to the 5th cycle without any significant loss of catalytic activity. After the 5th cycle, though, a significant loss of catalytic activity was observed (Fig 4).

The putative *N*-arylation mechanism is shown in Fig 5. Initially, the ligand DMAP binds to the copper in catalyst A, and then monovalent copper is inserted into the N—H bond of the aryl formamide through oxidative addition to form a copper coordination complex B. The arylboronic acid undergoes ligand exchange to obtain C through metal transfer reaction, and finally the coupling product is obtained after reduction elimination. At the same time, the monovalent copper catalyst is regenerated and enters a new catalytic cycle.

In summary, we have developed a highly efficient, green and simple method for synthesizing *N*-arylbenzamides starting from benzamide and phenylboronic acid by using Fe_3O_4-Cu_2O NPs as a

Table 2
Reaction of different benzamides and different phenylboronic acids[a].



Entry	Benzamide	Phenylboronic acid	Yield [b] %
1			80 **3a**
2			85 **3b**
3			82 **3c**
4			89 **3d**
5			79 **3e**
6			78 **3f**
7			71 **3g**
8			70 **3h**
9			85 **3i**
10			89 **3j**
11			65 **3k**
12			93 **3l**
13			90 **3m**
14			85 **3n**
15			87 **3o**
16			83 **3p**
17			86 **3q**
18			78 **3r**
19			68 **3s**

[a] Reaction conditions: phenylboronic acid (1 mmol), benzamide (0.5 mmol), KOH (2 mmol), Fe_3O_4-Cu_2O (30 mol%), DMAP (20 mol%), DMSO (2 mL), 100℃, 2 h, air. [b] Isolated yield.

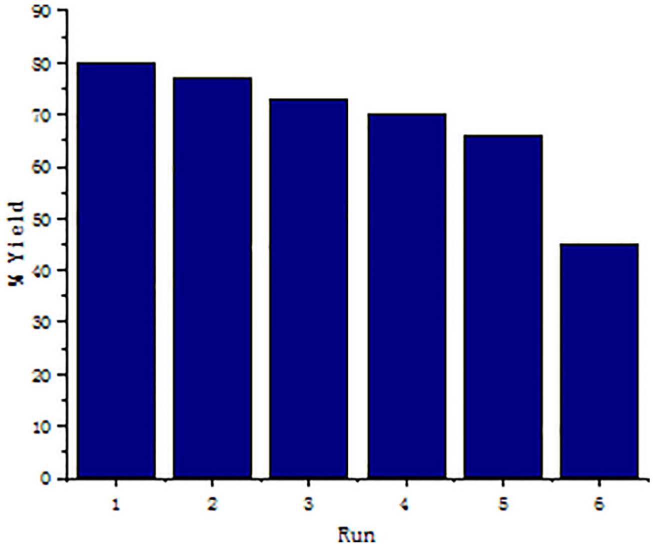


Fig 4. Reusability of Fe_3O_4-Cu_2O NPs.

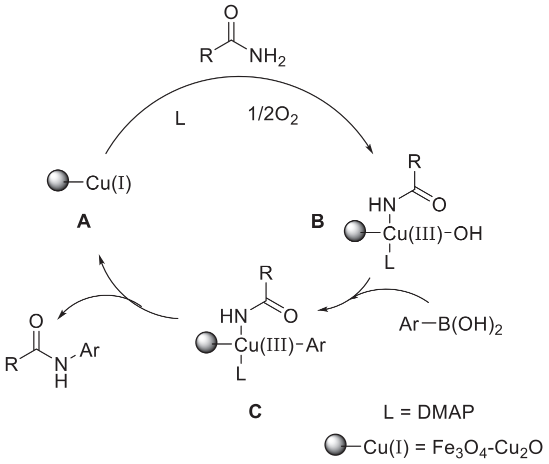


Fig 5. Proposed mechanism for *N*-arylation.

catalyst in the presence of DMAP as a ligand. A variety of *N*-arylbenzamides were obtained in good yield, and the catalyst can be quickly recovered by magnets, meeting the requirements of modern green chemistry. We believe this protocol can be used in medicinal chemistry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152327.

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