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Carbon–Heteroatom Bond Formation via Coupling Reactions Performed on a Magnetic Nanoparticle Bed

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Abstract: Cross-coupling reactions leading to carbon–heteroatom bonds yield compounds that attract substantial interest due to their role as structural units in many synthetic protocols for bioactive and natural products. Therefore, many research works aim at the improvement of heterogeneous catalytic protocols. We have studied the use of magnetite nanoparticles and solid base compounds in organic synthetic reactions in carbon–heteroatom bond formation because they can be flocculated and dispersed, and reversibly controlled by applying a magnetic field. In this work, we have developed an efficient and simple synthetic approach for the C–O/C–N cross-coupling reaction under ligand-free conditions by using CuI as a catalyst and KF/Fe_3O_4 as a base. We performed the nucleophilic aromatic substitution of electron-deficient aryl halides and phenols. It was found that both the solvent nature and the base have a profound influence on the reaction process. This approach affords good to excellent yields of arylated products. KF/Fe_3O_4 displayed convenient magnetic properties and could be easily separated from the reaction using a magnet and recycled several times without significant loss of catalytic activity. This method has been successfully investigated for the Ullmann coupling reaction.

Keywords: aromatic substitution; cross-coupling; diaryl ethers; heterogeneous catalysis; nanoparticles

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1. Introduction

Copper chemistry is extremely important because it can form Cu^0, Cu^I, Cu^{II}, and Cu^{III} oxidation states allowing one-electron or two-electron exchange. The different oxidation states can make useful interactions with different functional groups as Lewis acid or π-coordination. These features show remarkable activities allowing copper to catalyze different reactions [1].

Copper-complex catalytic materials have been successfully applied to cross-coupling reactions leading to carbon–heteroatom bonds. The chemicals thereby obtained attract substantial interest due to their important role as structural units in many synthetic protocols en route to bioactive and natural products [2–5].

Nucleophilic aromatic substitution (S_NAr) reaction is an important methodology for the preparation of diaryl ethers from activated aryl halides or phenols [6,7]; for example, the coupling of activated aryl halides with different phenolic substrates in the presence of potassium fluoride/Clinoptilolite (KF/CP) was studied by Hosseini et al. [8]. Compared to typical transition-metal-mediated processes for the formation of a carbon–heteroatom bond, the S_NAr reaction was found to be simple, showing mild reaction conditions, and was environmentally more convenient. An interesting alternative to this methodology is the coupling reaction of O, N, and S-arylation with 4-nitrochlorobenzene [9]. Recently, many researchers have aimed at the improvement of heterogeneous catalysts such as alumina-supported KOH, KF, and NaOH, transition-metal oxides [10–12], clay minerals or related materials [13,14], and zeolite-based catalysts [15,16]. Our interest in organic synthetic reactions developed by magnetite nanoparticle conditions prompted us to study the application of solid base compounds in carbon–heteroatom bond formation because they can be flocculated and dispersed and reversibly controlled by applying a magnetic field. By removing the external magnetic field, superparamagnetic nanoparticles can be dispersed completely in the reaction media, creating a vast surface that can be easily accessed by the substrate. Because of the high surface area and high catalytic activity, the practical utility of magnetic nanocomposites as catalysts has increased [17–24]. Nanomagnetic catalysts have been applied and studied widely in photocatalysts [25], biocatalysts [26], and phase-transfer catalysts [27]. Zhang and co-workers used nanoparticle Fe_3O_4-encapsulated CuO as a heterogeneous catalyst in the synthesis of diaryl ethers by the cross-coupling reaction; they also found that Fe_3O_4 alone did not show any catalytic effect [28]. Hu and co-workers reported a synthesis of the nanomagnetic catalyst KF/CaO–Fe_3O_4 by a facile impregnation method. The base catalyst KF/CaO–Fe_3O_4 was used to catalyze the transesterification of Stillingia oil and methanol for biodiesel production [29]. Using this method, we tried to prepare a nanomagnetic solid base catalyst KF/Fe_3O_4 that has an average particle diameter of ca. 20 nm. Other examples of the use of nanocatalysts in carbon-oxygen cross-coupling reactions for the synthesis of diaryl ethers can be found elsewhere [30]. Magnetic nanoparticles can selectively adsorb K ions and other alkali metal cations [29,31,32]. In the course of our previously published works for constructing of C–O/C–N bonds, we observed that KF impregnated on Fe_3O_4 (KF/Fe_3O_4) is a particularly useful and effective base for coupling reactions [8,33–37]. In a previous work, we found that the KF/Al_2O_3 combination provides a viable alternative to bases such as Cs_2CO_3, in the *N*-arylation of diazoles and the copper-catalyzed *N*-arylation of arylsulfonamides [33,38]. Here, the KF/Fe_3O_4 blend, which has the advantage of being separable with a magnet, along with an inexpensive Cu salt, can act satisfactorily in the C–O/C–N bond-formation reactions. The use of KF/Fe_3O_4 and CuX provides a synthesis with high selectivity in coupling reactions. We believe that KF supported on a magnetic Fe_3O_4 bed constitutes a good complement to other bases in copper-catalyzed coupling reactions. To the best of our knowledge, this is the first report on the use of KF/Fe_3O_4 in the C–N bond formation in the arylation of amides, carbazoles, and indoles and the synthesis of diaryl ethers.

2. Materials and Methods

2.1. Characterization

^1H and ^{13}C NMR spectra were recorded in Bruker Avance III spectrometer operating at 400.13 and 75.47 MHz, respectively; relevant spectra are available in the Supplementary Materials. Powder X-ray diffraction (XRD) was carried out on a Bruker ADVANCE-BRUKER D8 Discover (Cu K_ = 0/15,406 nm). The scanning rate was 1 min^{-1} in the 2Θ? range from 20 to 80°. Scanning electron microscopy (SEM) was recorded on a Hitachi S-1460 electron microscope, using an accelerating voltage of 200 kV. Melting points were determined using an Electrothermal IA 9100 Digital Melting Point apparatus. Thin-layer chromatography (TLC) was performed using 60 mesh silica gel Merck TLC plates. Flash column chromatography was performed with Merck silica gel (230–400 mesh). Reactions were carried out under air conditions.

2.2. Preparation of Fe_3O_4 Superparamagnetic Nanoparticle MNPs

Co-precipitation of $FeCl_3.6H_2O$ and $FeCl_2{\cdot}4H_2O$ in ammonia was applied for MNP preparation, according to a procedure described elsewhere [39]. $FeCl_3{\cdot}6H_2O$ (5.41 g, 20 mmol) and $FeCl_2{\cdot}4H_2O$ (2 g, 10 mmol) were dissolved in 100 mL deionized water under argon atmosphere at 90 °C; then, ammonium hydroxide 25% solution (20 mL) was added with vigorous mechanical stirring. After 20 min, the color of the bulk solution turned black. The resulting black MNPs were separated by applying a permanent external magnet, washed three times with deionized water, and then dried under vacuum at 60 °C for 12 h.

2.3. Preparation of KF/Fe_3O_4

This catalyst was prepared by mixing KF (2.5 g) and Fe_3O_4 (0.5 g) in a mortar. The mixture was transferred to a flask and vacuum-dried in an oil bath at 120–130 °C for 7 h. The resulting KF/Fe_3O_4 was kept in a desiccator until required.

2.4. General Procedure for the Synthesis of C–N Materials

Copper (I) iodide (19 mg, 10 mol%) and KF/Fe_3O_4 (160 mg) were added to a magnetically stirred mixture of nitrogenated compound (1.5 mmol) and aryl halide (1 mmol) in DMF (5 mL). The reaction mixture was then heated at 120 °C for the specified time. The reaction progress was monitored by TLC. The reaction mixture was allowed to cool down to room temperature, filtered, and then partitioned between ethyl acetate (3 mL) and saturated aqueous NaCl solution (3 × 10 mL). The organic fraction was washed with water (3 × 10 mL), dried with sodium sulphate, filtered, and concentrated in a rotary evaporator. The crude product was purified by column chromatography using hexane and ethyl acetate (8:2) as eluent to afford the pure product. The melting points and spectroscopic data for the known products were identical to those reported in the literature.

2.5. General Procedure for the Synthesis of Diaryl Ethers

Procedure A. Cu-catalyzed coupling of aryl iodides with phenols in DMF solvent: A screwcap, oven-dried tube was charged with the corresponding phenol (1.3 mmol), iodobenzene (1 mmol), KF/Fe_3O_4 (160 mg), and CuI catalyst (0.1 mmol). The tube was septum-capped, air evacuated, and back-filled with argon. Anhydrous DMF (5 mL) was added, and the reaction mixture was stirred at 120 °C for 6 h (the progress of the reaction was monitored by TLC). After the complete disappearance of the iodobenzene, the mixture was cooled to room temperature, diluted with ethyl acetate, filtered, and the crude was purified by column chromatography on silica gel (ethyl acetate/hexane) to obtain the desired product.

Procedure B. Coupling of aryl fluorides/aryl chlorides with Phenols in DMF solvent: A mixture of the phenol (1.3 mmol), the appropriate aryl halide (1.2 mmol), and KF/Fe_3O_4 (160 mg), in DMF as a solvent (5 mL), was heated to 120 °C and stirred under air conditions until the completion of the reaction (monitoring by TLC or GC). The mixture was cooled to room temperature, diluted with ethyl acetate, and filtered. The resulting solution was placed in a separating funnel and washed twice with H_2O. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting products were purified either by column chromatography on silica gel (ethyl acetate/hexane) or recrystallization (in methanol).

3. Results and Discussion

3.1. Characterization of the Catalyst

The X-ray diffraction pattern of magnetic nanoparticles (MNPs) can be seen in Figure 1. Sharp and strong peaks indicate good sample crystallinity. The patterns at 2Θ values 30.1°, 35.4°, 43.1°, 53.4°, 57°, and 62.6° can be assigned to (220), (311), (400), (422), (511) and (440) crystal planes in Fe_3O_4 cubic lattice, which agree with the standard Fe_3O_4 (Joint Committee on Powder Diffraction Standards Card No 19-0629).

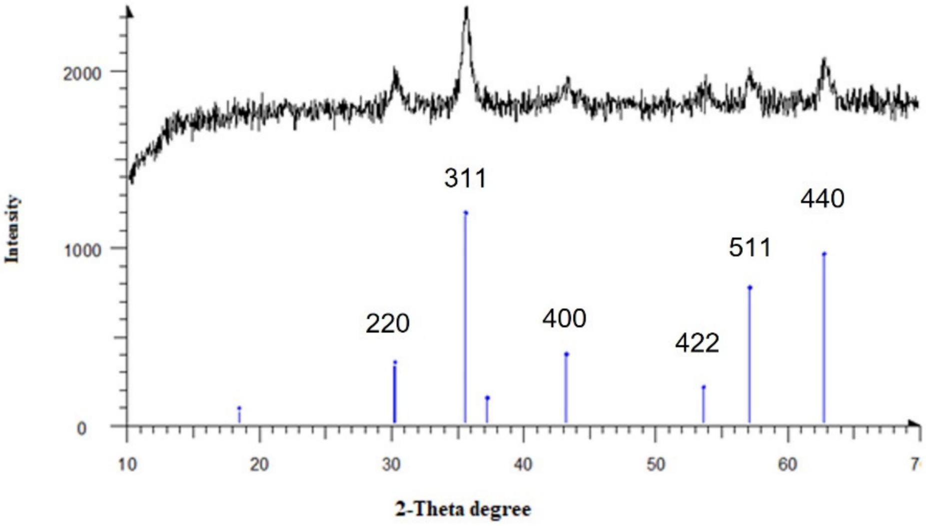
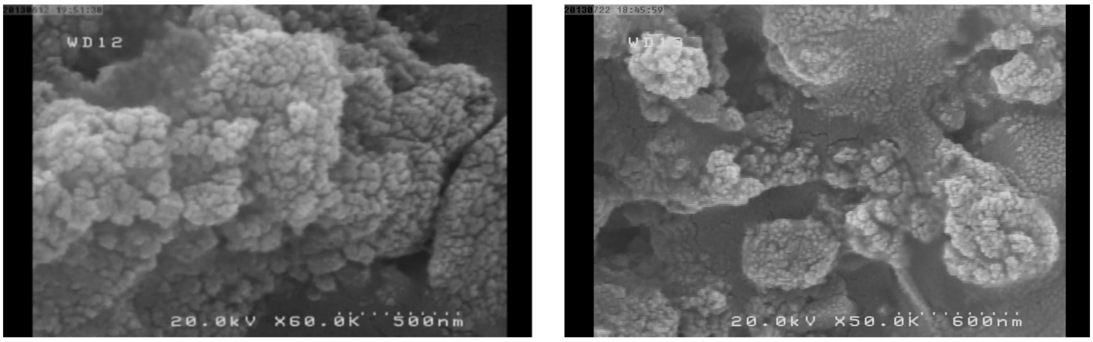


Figure 1. XRD patterns of the MNPs.

Scanning Electron Microscopy (SEM) analysis (Figure 2) of the KF/Fe_3O_4 showed uniform-sized particles before and after four reaction cycles with spherical morphology with an average size range of 20 nm.

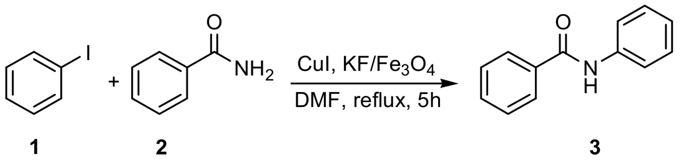


(**a**) (**b**)

Figure 2. SEM Images of synthesized (**a**) KF/Fe_3O_4 and (**b**) KF/Fe_3O_4 after 4 cycles.

3.2. Formation of C–N Bond

In our study, we initially addressed the optimization of the ratio of KF to Fe_3O_4, taking as a model the synthesis of benzanilide by cross-coupling the reaction of iodobenzene and benzamide in the presence of CuI in DMF at reflux as solvent (Scheme 1). The results are shown in Table 1.



Scheme 1. Model reaction for the C–N bond formation.

Table 1. Optimization of the KF to Fe_3O_4 ratio in the synthesis of benzanilide (**3**) [a].

Entry	KF (g)	Fe_3O_4 (g)	KF/Fe_3O_4 (g:g)	Yield % [b]
1	0.5	1	0.5	20
2	1	0.5	2	60
3	2	0.5	4	85
4	2.5	0.5	5	90
5	3	0.5	6	90

[a] Reaction Conditions: PhI (1) (1 mmol), Benzamide (2) (1.5 mmol), refluxing DMF (5 mL), CuI (15 mol%). [b] Isolated yield.

First, we used the CaO/Fe_3O_4 blend, but it resulted in low yields. So, we decided to change the base to KF. Since KF is moisture sensitive, we prepared dry KF/Fe_3O_4 under vacuum at 70 °C. Some research has been conducted in the presence of a CuI catalyst, a strong base or a ligand, but it is not similar to our method. The new system (KF/Fe_3O_4) produced promising results, justifying a more extended study on its scope.

As can be seen in Table 1, when increasing the impregnated proportion of KF to Fe_3O_4, the yield of product increases too; these results may be assigned from increased adsorption of fluoride anions on the Fe_3O_4 surface. In Entry 4, Table 1 contains the ratio of KF to Fe_3O_4 (5 g/1 g) selected for further experiments.

To gain insight into the effect that solvent, temperature, CuI load and L-proline have on the reaction outcome, several experiments were run using the model reaction shown in Scheme 1. It is worth noting that L-proline is known to act as a ligand in the catalytic system CuI/L-proline [40]. The conditions and results are shown in Table 2.

Table 2. Optimization of the reaction conditions for the synthesis of benzanilide (**3**) [a].

Entry	Solvent	T (°C)	CuI (mol%)	L-Proline (mol%)	Yield (%) [b]
1	o-Xylene	Reflux	15	-	Trace
2	Toluene	Reflux	15	-	Trace
3	THF	Reflux	15	-	Trace
4	Dioxane	Reflux	15	-	20
5	DMSO	Reflux	15	-	80
6	DMF	Reflux	15	-	90
7	DMF	Reflux	10	10	90
8	DMF	Reflux	5	10	60
9	DMF	120	15	-	90
10	DMF	120	10	-	90
11	DMF	80	15	-	30
12	DMF	r.t.	15	-	Trace

[a] Reaction conditions: Iodobenzene (1) (1 mmol), benzamide (2) (1.5 mmol), solvent (5 mL), KF/Fe_3O_4 (160 mg). [b] Isolated yield.

It is worth pointing out that the reaction between **1** and **2** mediated by either KF or Fe_3O_4 alone did not proceed. As the results in Table 2 show, it was found that the solvent has a remarkable influence on the reaction success. In either *o*-xylene, toluene, or THF, only a trace amount of product was obtained (Table 2, Entries 1–3), whereas, in dioxane, DMSO, and DMF, 20%, 80%, and 90% yield of the desired product was obtained, respectively (Table 2, Entries 4–6). Then, we performed this reaction in the presence of 10 mol% L-proline and 5 mol% and 10 mol% copper (I) iodide (Table 2, Entries 7 and 8), but no real improvement was found compared to the ligand-free experiment. Moreover, several experiments were carried out to check the influence of the temperature. At 80 °C and room temperature, low yield or traces of products were obtained (Table 2, Entries 11 and 12). Conducting the reaction at 120 °C with either 10 mol% or 15 mol%, excellent yields of CuI were obtained (Table 2, Entries 9 and 10); therefore, we chose the conditions shown in Entry 10 of Table 2.

After optimization of the protocol, we subjected aryl halides for C–N bond formation in the arylation of amides, carbazoles, and indoles. The reagents used are shown in Figure 3 and the results are listed in Table 3.

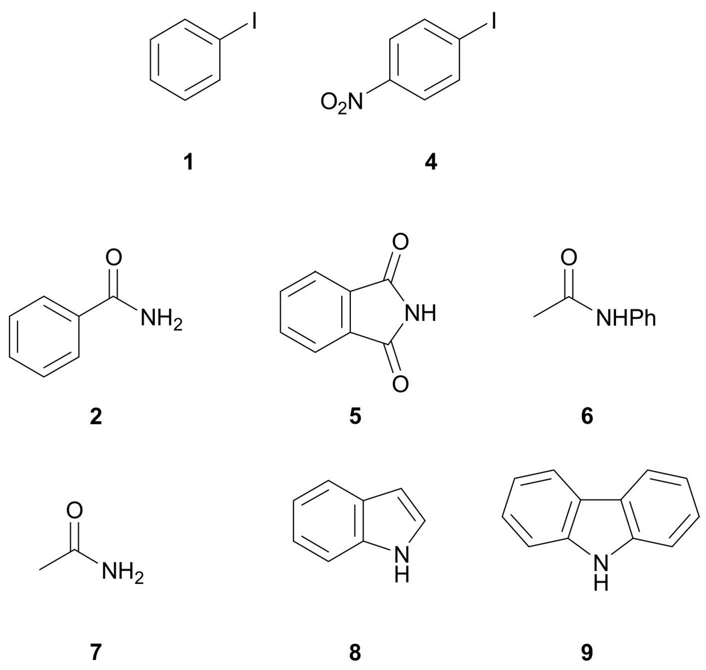


Figure 3. Reagents used for arylation of amides.

Table 3. CuI-catalyzed coupling of aryl halide and nitrogen containing compounds [a].

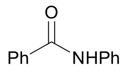
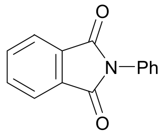
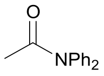
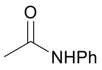
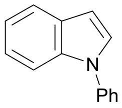
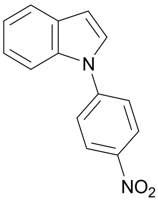
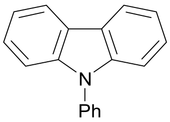
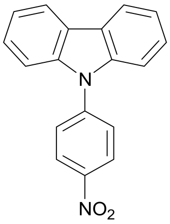
Entry	Aryl Iodide	Nitrogenated Compound	Product	Time (h)	Yield (%) [b]
1	**1**	**2**	 **3**	5	90
2	**1**	**5**	 **10**	7	90
3	**1**	**6**	 **11**	7	80
4	**1**	**7**	 **12**	6	85
5	**1**	**8**	 **13**	7	90

Table 3. *Cont.*

Entry	Aryl Iodide	Nitrogenated Compound	Product	Time (h)	Yield (%) [b]
6	**4**	**8**	 **14**	6	90
7	**1**	**9**	 **15**	3	90
8	**4**	**9**	 **16**	2	90

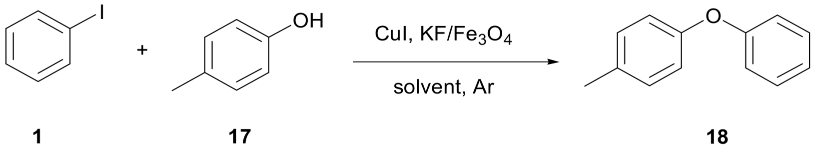
[a] Reaction conditions: Aryl iodide (1 mmol), nitrogenated compound (1.5 mmol), DMF (5 mL), 120 °C, CuI (10 mol%), KF/Fe_3O_4 (160 mg). [b] Isolated yield.

According to the results shown in Table 3, indole, carbazole, and amide compounds were successfully transformed to the corresponding *N*-aryl compounds. The reactions of carbazole and indole with iodo- and 4-nitroiodobenzenes under optimum reaction conditions gave excellent yields (Table 3, Entries 5–8). Moreover, the amidation reaction carried out under similar reaction conditions, gave good yields of *N*-phenylamide (Table 3, Entries 1–4).

In addition to the magnetic base, ligand-free protocols also have great efficiency in Ullmann coupling reactions. During the past few years, considerable research reported the efficiency of the Ullman reaction using copper salts with several ligands for the preparation of diaryl ethers [39,41–52].

3.3. Formation of C–O Bond

Next, we investigated the strategy by copper (I) salt as a catalyst and KF/Fe_3O_4 as a base/bed in the reaction of iodobenzene (**1**) with *p*-cresol (**17**) to form 1-methyl-4-phenoxybenzene (**18**) as a model procedure in different solvents (Scheme 2); the results are listed in Table 4.



Scheme 2. Synthesis of diaryl ethers.

Table 4. Optimization of the reaction conditions for the synthesis of 1-methyl-4-phenoxybenzene (**18**) [a].

Entry	Solvent	T (°C)	CuI (mol%)	L-Proline (mol%)	Yield (%) [b]
1	*o*-Xylene	Reflux	15	-	Trace
2	Toluene	Reflux	15	-	Trace
3	THF	Reflux	15	-	Trace
4	Dioxane	Reflux	15	-	30
5	DMSO	Reflux	15	-	80
6	DMF	Reflux	15	-	95
7	DMF	120	15	-	95
8	DMF	80	15	-	30
9	DMF	r.t.	15	-	Trace
10	DMF	120	10	-	95
11	DMF	120	5	5	70
12	DMF	120	10	10	95

[a] Reaction conditions: PhI (**1**) (1 mmol), *p*-Cresol (**17**) (1.3 mmol), solvent (5 mL), KF/Fe_3O_4 (160 mg), 3 h in argon atmosphere. [b] Isolated yield.

As shown in Table 4, it was found that the solvent has a profound effect on the yield of the product. As before, the reaction was performed without a ligand. When we used *o*-xylene, toluene, and THF, only a trace amount of product was obtained (Table 4, Entries 1–3), but in dioxane, DMSO, and DMF, 30%, 80%, and 95% yields of the desired product were obtained, respectively (Table 4, Entries 4–6). First, to optimize the amount of catalyst, we examined 15 and 10 mol% of copper (I) iodide in refluxing DMF. The reaction was performed satisfactorily using these conditions and yielded corresponding *N*-aryl compounds (Table 4, Entries 6 and 10). Moreover, note that the use of 10 mol% of L-proline in conjunction with 10 mol% of CuI did not improve the reaction outcome (Table 4, compare Entries 12 and 10).

Using optimized reaction conditions (Table 4), we carried out the reaction between aryl iodides and phenols to extend the scope of this protocol of synthesis of diaryl ethers using the reagents shown in Figure 4. The results are listed in Table 5.

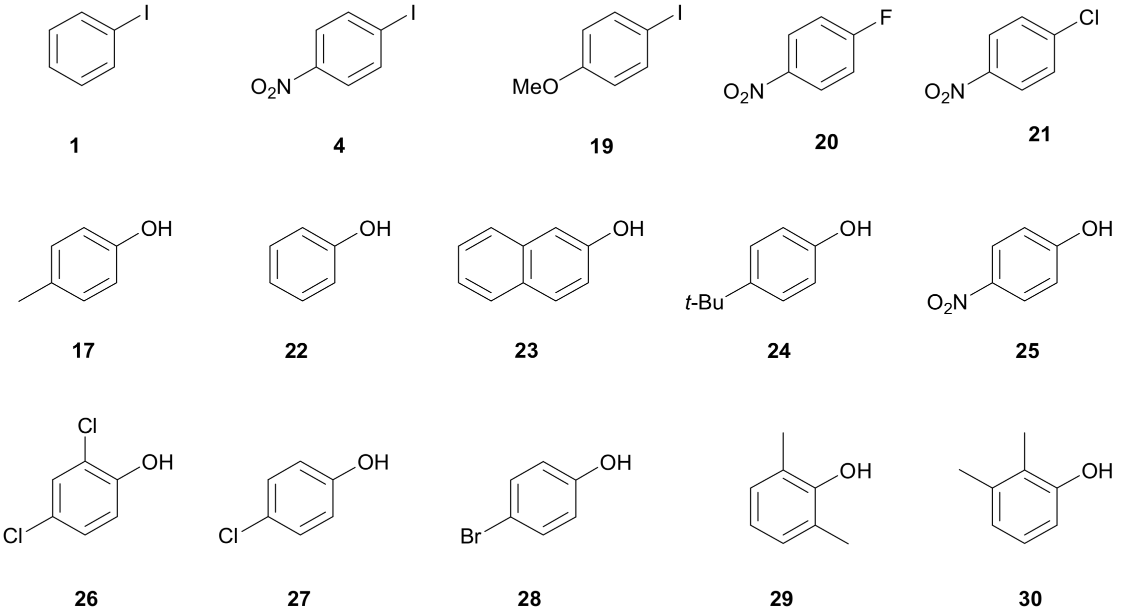
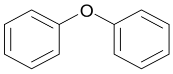
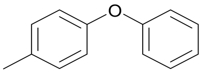
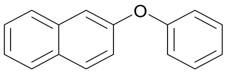
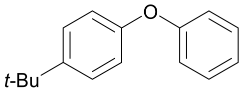
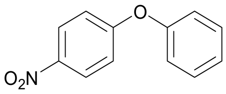
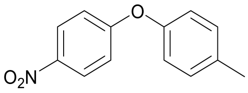
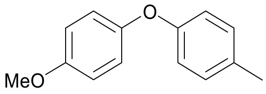
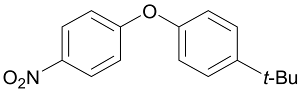
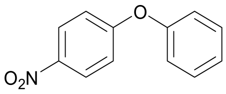


Figure 4. Reagents used for the synthesis of diaryl ethers.

Table 5. Coupling of aryl iodides with phenols catalyzed by CuI [a].

Entry	Aryl Iodide	Phenol	Product	Time (h)	Yield (%) [b]
1	**1**	**22**	 **31**	5	95
2	**1**	**17**	 **18**	5	95
3	**1**	**23**	 **32**	5	88
4	**1**	**24**	 **33**	5.5	95
5	**4**	**25**	 **34**	4	95
6	**4**	**17**	 **35**	4	92
7	**18**	**17**	 **36**	3.5	90
8	**4**	**24**	 **37**	4	95
9	**1**	**25**	 **34**	12	95

[a] Reaction conditions: Aryl iodide (1 mmol), phenol (1.3 mmol), DMF (5 mL), 120 °C, CuI (20 mg), KF/Fe_3O_4 (160 mg), in argon atmosphere. [b] Isolated yield.

When the results from Entries 5 and 9 in Table 5, in which the same product (**34**) is formed, are compared, it becomes obvious that there is an accelerating effect when the electron-withdrawing group is in the iodide rather than in the phenol since the same yield is obtained in 4 h (Table 5, Entry 5) as opposed to 12 h (Table 5, Entry 9).

This protocol provides an outstanding entry to diaryl ethers, no matter whether the groups in either the iodide or the phenol are electron-withdrawing or electron-donating or neither. It is worth noting that when the phenolic compound carries an electron-withdrawing group, the reaction is slower but still proceeds with excellent yield (Table 5, Entry 9). In Entries 5, 6, and 8 in Table 5, 1-iodo-4-nitrobenzene reacted quantitatively in 4 h with phenols with no substitution or a *p*-alkyl moiety. Furthermore, when iodobenzene is reacted with phenol, *p*-cresol, 2-naphthol, and 4-*tert*-butylphenol, the reaction yields are excellent, taking 5 h to complete (Table 5, Entries 1–4); nevertheless, the reaction takes up to 12 h when the reactant is 4-nitrophenol, as mentioned before (Table 5, Entry 9). Finally, 1-iodo-4-methoxyphenol and *p*-cresol produce the corresponding diaryl ether in 90% yield in only 3.5 h (Table 5, Entry 7).

In continuation to our studies on the reaction between phenols and nitro-activated aryl halides, we investigated the scope of this reaction by coupling various phenolic nucleophiles with 1-fluoro- and 1-chloro-4-nitrobenzene. Remarkably, after optimizing the reaction conditions, we found that the reactions could not only proceed in excellent yields in air atmosphere but also with no need for a copper catalyst whatsoever. The base/bed, KF/Fe_3O_4, along with the right solvent choice, was enough to promote the reaction with these substrates (Tables 6 and 7). It is worth noting that the hydrogen halide eventually formed will be neutralized and the excess molecules will be lost to the atmosphere, where they will react with moisture or oxygen.

Table 6. Coupling of 1-fluoro-4-nitrobenzene (**20**) with phenols catalyzed by KF/Fe_3O_4 [a].

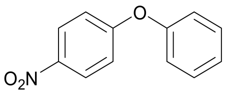
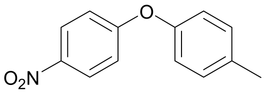
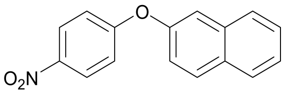
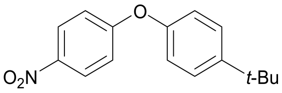
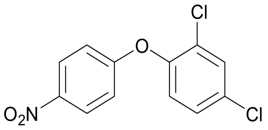
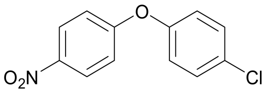
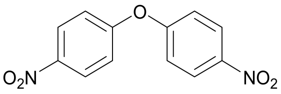
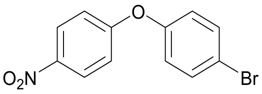
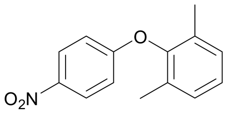
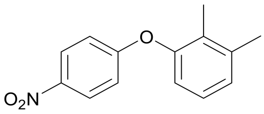
Entry	Phenol	Product	Time (min)	Yield (%) [b]
1	**22**	 **34**	10	95
2	**17**	 **35**	10	95
3	**23**	 **38**	25	88
4	**24**	 **37**	50	95
5	**26**	 **39**	30	95
6	**27**	 **40**	20	92
7	**25**	 **41**	60	90
8	**28**	 **42**	25	95

Table 6. *Cont.*

Entry	Phenol	Product	Time (min)	Yield (%) [b]
9	**29**	 **43**	15	95
10	**30**	 **44**	45	95

[a] Reaction conditions: Aryl fluoride (1.2 mmol), phenol (1.3 mmol), DMF (5 mL), 120 °C, KF/Fe_3O_4 (160 mg).
[b] Isolated yield.

Table 7. Coupling of 1-chloro-4-nitrobenzene (**21**) with phenols catalyzed by KF/Fe_3O_4 [a].

Entry	Phenol	Product	Time (h)	Yield (%) [b]
1	22	**34**	1.5	90
2	17	**35**	0.9	95
3	23	**38**	4.5	85
4	24	**37**	5	90
5	26	**39**	3	95
6	27	**40**	4.5	90
7	25	**41**	5	85
8	28	**42**	4.5	92
9	29	**43**	1.5	94
10	30	**44**	3	90

[a] Reaction conditions: Aryl chloride (1.2 mmol), phenol (1.3 mmol), DMF (5 mL), 120 °C, KF/Fe_3O_4 (160 mg).
[b] Isolated yield.

As a result, it is shown that the nucleophilic aromatic substitution between active aryl halides and phenols can be performed under mild conditions to prepare diaryl ethers. The coupling of activated aryl fluorides with various phenols gives the corresponding product in excellent yields; when electron-rich groups are present in the *para* or *orto* position of phenols, excellent yields are obtained in a short time.

3.4. Role of the Copper and Recyclability of the Catalyst

As stated in the literature [33,38], the role of the ligand in this type of chemical transformation is to activate the copper catalyst to dissolve and start the reaction process. In the reaction that we have studied, the copper is activated in the presence of the solvent and enters the catalytic reaction cycle without the presence of a ligand. The reaction mechanism is shown in Figure 5. The reaction has a two-step catalytic cycle: oxidative addition and reductive elimination. In the first step, the copper catalyst is oxidized by bonding to the reactants, and in the second step, the reactants are converted to the products, and copper is reduced back and so the cycle continues.

The recyclability of the magnetic catalyst was examined for the reaction of iodobenzene (1a) and benzamide (2a) to give benzanilide (3a) and the synthesis of 1-(4-nitrophenoxy)-4-methylbenzene (3x) by a reaction between 1-chloro-4-nitrobenzene (1b) and *p*-cresol (2b). After the completion of either reaction, the catalyst could be simply separated with a magnet, and then recycled at least three times with no significant change in its catalytic activity (Table 8).

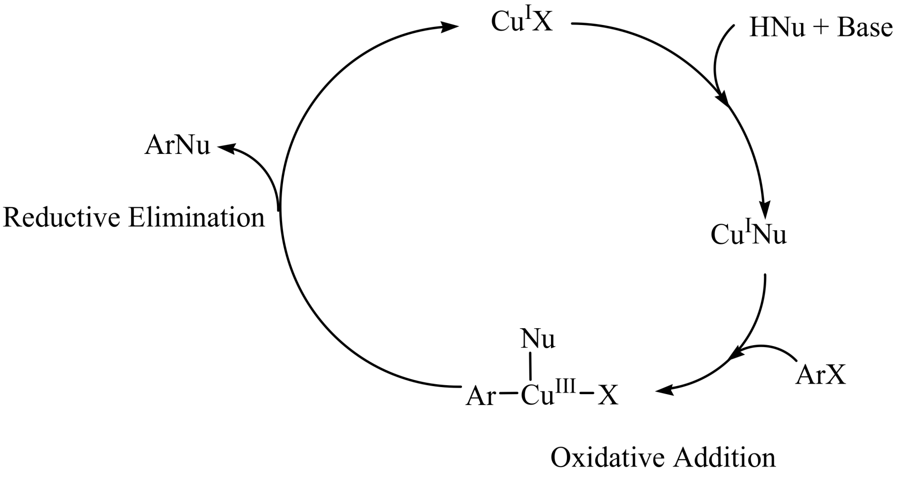


Figure 5. Catalytic cycle.

Table 8. Recyclability of KF/Fe_3O_4 in the synthesis of **3** [a] and **35** [b].

Reaction Cycle	Yield (%) 3 [c]	Yield (%) 35 [c]
1	90	95
2	90	95
3	88	90
4	84	88

[a] Reaction conditions: Iodobenzene (**1**) (1 mmol), benzamide (**2**) (1.5 mmol), DMF (5 mL), 120 °C, CuI 10 mol%, KF/Fe_3O_4 (160 mg). [b] Reaction conditions: 1-Iodo-4-nitrobenzene (**4**) (1.2 mmol), *p*-cresol (**17**) (1.3 mmol), DMF (5 mL), 120 °C, KF/Fe_3O_4 (160 mg). [c] Isolated yield.

4. Conclusions

This work evaluated the subject of heteroatom coupling reactions with active alkyl halides in SNAr substitution reactions.

In conclusion, the copper-catalyzed coupling reaction can be performed using stable CuI as a copper source in the presence of KF/Fe_3O_4 as a base. This is a simple, inexpensive, and efficient method for the coupling of carbon and heteroatoms. We have developed a new and simple strategy for constructing carbon–heteroatom bonds, such as C–O and C–N bonds. The reaction is performed in the presence of KF/Fe_3O_4, which acts as a magnetic base, and CuI as a catalyst without using any ligand compared to the same synthetic procedure. This method provides an efficient route for the preparation of diaryl ethers from phenols and aryl halides. The formation of C–N bonds via the Ullmann protocol is also achieved. In fact, in this article, a new and effective method in coupling reactions is designed and optimized.

The advantage of this method over previous methods is that our reaction is performed in the presence of a nanomagnetic substrate (bed) that shows selective adsorption to potassium ions and other metal cations. Furthermore, the reaction was performed as an experimental technique in which no organic ligand was used, and the reaction was carried out under mild conditions. We conclude that the KF/Fe_3O_4 blend is able to produce a synthesis with high selectivity in coupling reactions. For example, compared to a catalyst such as KF/Al_2O_3, our material seems to be a better option for performing chemical reactions with the same reactive materials. We believe that KF supported on magnetic Fe_3O_4 provides an excellent complement to other bases in copper-catalyzed coupling reactions, which have already been utilized in several works.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/appliedchem1020007/s1. Figure S1: NMR spectra obtained for benzanilide (compound **3**), Figure S2: NMR spectra obtained for *N*-Phenylindole (compound **13**), Figure S3: NMR spectra obtained for *N*-Phenylcarbazole (compound **15**), Figure S4: NMR spectrum obtained for 1-Methyl-4-phenoxybenzene (compound **18**), Figure S5: NMR spectrum obtained for Diphenyl ether (compound **31**), Figure S6: NMR spectra obtained for 1-Nitro-4-phenoxybenzene (compound **34**), Figure S7: NMR spectra obtained for 4-Methyl 4-nitro-diphenyl ether (compound **35**), Figure S8: NMR spectra obtained for 1-(4-Nitrophenoxy)-4-*tert*-butylbenzene (compound **37**), Figure S9: NMR spectra obtained for 1-(2,4 Dichlorophenoxy)-4-nitrobenzene (compound **39**), Figure S10: NMR spectra obtained for 1-(4-Chlorophenoxy)-4-nitrobenzene (compound **40**), Figure S11: NMR spectra obtained for 1-(4-Nitrophenoxy)-4-nitrobenzene (compound **41**), Figure S12: NMR spectrum obtained for 1-Bromo-4-(4-nitrophenoxy)benzene (compound **42**).

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