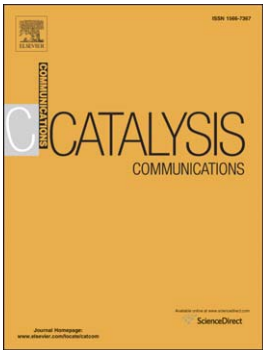

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A copper-free Sonogashira reaction using nickel ferrite as catalyst in water

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Abstract

The Sonogashira reaction using nickel ferrite nanoparticles as catalyst and under copper-free conditions was investigated in water as a green solvent. Various types of aryl and alkyl halides were successfully coupled with phenyl acetylene under the optimized reaction conditions with very good to excellent yields at short time. The catalyst is easily recoverable and can be reused for several runs with good turnover number.

Keywords: Sonogashira reaction, nickel ferrite nanoparticles, water, super paramagnetism

1.1 Introduction

Compounds containing carbon- carbon triple bonds have found applications in diverse areas including pharmaceuticals, natural products, bioactive compounds, engineered materials and molecular organic materials [1-3]. From the synthetic points of view, the Sonogashira reaction ranks among the most valuable and straightforward processes for the formation of terminal and internal alkynes [4-6].

Despite the presence of large amounts of reports regarding to coupling of aryl, alkenyl and alkynyl halides using transition metal catalysts, examples of coupling of alkyl halides are very rare [7-12]. This is attributed to more electron-rich nature of alkyl halides compared to sp- and sp^2- hybridized carbon electrophiles making the oxidative-addition step of the reaction difficult. Furthermore, the β-H elimination step of the reaction to give olefinic compounds is also prone to be difficult using alkyl halides as one of the coupling partners [13].

Traditionally, this reaction requires a large amount of palladium and CuI as co-catalyst to catalyze the reaction between sp^2-C halides and terminal acetylenes [14]. The presence of Cu/O_2 in the reaction media can cause to a side reaction of Glaser-type dimerization of acetylene substrates to afford diyne [2, 15] as well as contamination of the products with poisonous metal residues [16]. This is one of the main drawbacks of the Sonogashira reaction that has been partially solved employing copper-free reactions [17, 18]. Most catalytic systems used for the Sonogashira reaction are homogeneous palladium-based catalysts having tedious recovery, if not impossible [19]. To solve this problem, researchers have attracted many attentions to develop new catalytic systems with high efficiency and easy recovery [13, 20, 21].

Bimetallic nanomaterials are an important class of heterogeneous catalysts with well-defined size, shape and composition properties [22, 23]. In these compounds, the addition of the second metal has a significant effect on geometric and electronic structure of nanoparticles causing to their better catalytic activity, selectivity and stability [24]. $NiFe_2O_4$ nanoparticles, one of the known bimetallics, show very good catalytic activity in organic reactions [25]. These nanoparticles show superparamagnetic properties making it possible to recover them using an external magnetic field after completion of the reaction.

The original Sonogashira reaction was generally performed in organic solvents as reaction media; but these solvents suffer from safety, health and environmental issues because of their toxicity, flammability and volatility. Considering the large amounts of solvents used in organic reactions, this is the main drawback for most chemical industries. So, there is increasing interest to search for finding new methodologies to perform reactions under solvent-free conditions or in water in order to comply with the Green Chemistry principles [14, 26, 27]. However, the application of water for such chemical transformation is seldom reported [28]. Approximately, in most of these reports, the reactions need to a long times (about 24 h) to be completed with moderate to good yields.

A small glance to the literatures shows clearly the absence of enough researches on the C_{sp}-alkyl halide coupling reaction in the presence of transition metal catalysts. Historically, in 2003, Fu *et al.* [29] reported for the first time the palladium-catalyzed reaction of alkyl bromides and iodides with alkynes (Scheme 1a). However, these conditions were not applicable for alkyl chlorides and also, the reactions needed long times and resulted in moderate yields. Furthermore, this reaction required CuI as co-catalyst causing to the formation of some diyne as by-product. Lately, in 2009, Hu *et al.* [30] described firstly the Sonogashira coupling of alkyl halides using a nickel-based homogeneous catalytic system (Scheme 1b). Again in this case, it was necessary to use CuI to improve the reaction conditions. The time required for the completion of these reactions is also too long. Both of these reactions were conducted in the presence of hazardous organic solvents. Another main drawback of these reactions was the homogeneous nature of their catalysts making their recovery difficult.

((Scheme 1))

Herein, in continuation of previous works and in order to show the applicability of the previously synthesized catalytic system in diverse organic reactions [31-33], we wish to report a copper-free Sonogashira reaction of different aryl and alkyl halides with phenylacetylene using a highly active recyclable heterogeneous catalyst, $NiFe_2O_4$, under conventional heating conditions in water as a green solvent (Scheme 1c). Because of the nanosized characteristic of this catalyst, all reactions can be performed efficiently using small amount of the catalyst in short times compared to the most reported Sonogashira reactions using the straightforward reaction conditions.

1.2 Experimental

1.2.1 Materials and characterization methods

All materials used are commercially available and were purchased from Merck and used without any additional purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker (Avance DRX-500) spectrometer using $CDCl_3$ as solvent at room temperature. Chemical shifts δ were reported in ppm relative to tetramethylsilane as an internal standard. XRF analysis was recorded on Spectro Xepos Spectrometer. The characterization of the samples was done by crystallographic phase identification performed on a Sradi P diffractometer with Cu Kα radiation, a graphite monochromator on the diffracted beam and oscillation counter. FTIR spectra of samples were taken using an ABB Bomem MB-100 FTIR spectrophotometer. The morphology of the catalyst was observed using a Philips XL30 scanning electron microscope (SEM). Magnetic measurements were carried out at room temperature and by using an AGFM magnetometer.

1.2.2 General Procedure for the Sonogashira Reaction

In a round-bottom flask equipped with a condenser for refluxing and a magnetic stirring bar, aryl/ alkyl halide (1 mmol), phenyl acetylene (1 mmol), K_2CO_3 (1.1 mmol), nickel ferrite nanoparticles (0.05 mmol) and water (3 ml) were added and heated at 100°C under air atmosphere. The mixture was vigorously stirred under these reaction conditions and its completion was monitored by TLC (EtOAc–n-hexane, 25:75).

In each case, after completion of the reaction, the mixture was diluted with diethyl ether and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure using a rotary evaporator. The residue was purified by recrystallization from ethanol and water.

1.3 Results and Discussion

The nanoparticles of nickel ferrite were prepared according to the procedure previously reported by our group [31]. After identification and characterization of the exact structure of the catalytic system, its activity in the Sonogashira reaction was investigated under conventional heating conditions.

For optimization of reaction conditions, the coupling of bromobenzene with phenylacetylene as the model reaction was chosen and the effects of the base, solvent and concentration of catalyst on the reaction were examined. The results are shown in Table 1. Firstly, different solvents were employed in this reaction using K_2CO_3 as base and in the presence of 5 mol% of catalyst (entries 1-4). The results clearly showed that water can be used as reaction media as well as hazardous organic solvents. So, in order to comply with Green Chemistry principles, water was selected as the best solvent for this reaction (entry 4).

((Table 1))

The type of base employed in these reactions also can affect their yields. So, in the next step, various types of organic and inorganic bases were investigated (entries 4-8). Among the bases used, both K_2CO_3 and Cs_2CO_3 have the same effects and can conduct the reaction effectively. So, considering more availability of K_2CO_3 and its lower price, it was chosen as the optimum base for the reaction (entry 4).

The amount of the $NiFe_2O_4$ required for catalyzing the reactions was optimized in the next step. To this end, reaction of phenylacetylene and bromobenzene was carried out both in the absence and also in the presence of 0.1, 1, 2, 5 and 10 mol% of the catalyst (entries 4, 9-13) and finally it was demonstrated that use of 5 mol% of catalyst can effectively catalyze the reaction in a short time with a reasonable yield (entry 4).

Another parameter that considerably could affect the reaction was temperature. So, its effect was also examined by performing the model reaction at room temperature, 60 and 100 ^{o}C (entries 4, 14-15). According to the results shown in table 1, the reaction can be carried out optimally at 100 ^{o}C resulting in higher conversion during shorter times.

With our optimized reaction conditions in hand, the scope of the Sonogashira reaction was investigated. The results are summarized in Table 2. As can be seen, different types of aryl halides bearing both electron-donating and electron-withdrawing groups can be coupled effectively with phenyl acetylene under the defined conditions. Although it is often reported that the reactivity of aryl chlorides in the coupling reactions is low, employing these conditions can conduct the reaction between various types of aryl chlorides as well as aryl iodides and bromides. It is a noteworthy point because of more availability and abundance of aryl chlorides. Observing the excellent activity of the catalytic system under the defined reaction conditions, in the next step, the reaction of some activated alkyl halides was investigated. Again, the results were surprising and all the reactions were completed in short times with very good yields.

Although active alkyl halides were successfully coupled with phenylacetylene (entries 16-18), the yields of the reaction of inactive alkyl halides were not high enough (entries 19-22). In fact, the reaction of these alkyl halides such as 1-bromopropan, 2-bromopropane, 1-chlorobutane and iodoethane requires longer times to be completed. Furthermore, due to the formation of small amount of byproducts, the final yields of these reactions decreased.

Also, phenyl acetylene was substituted with 1- heptyne as the second coupling partner with some aryl halides to show further the scope of the procedure. In these cases, again good conversions in short times were gained (entries 23-26).

((Table 2))

In order to examine the applicability of the defined procedure, a large scale reaction was performed successfully between 3 mol (600 mg) of 4-bromoacetophenone and 3 mol (330 mL) of phenyl acetylene under optimized reaction conditions (Scheme 2).

((Scheme 2))

To check the reusability of the catalyst, the reaction of bromobenzene with phenyl acetylene was performed under the optimized reaction conditions. After measuring its yield, the superparamagnetic nanoparticles of the catalyst were separated using a magnet. These nanoparticles after washing with water and drying on air were employed in the same reaction for the second run. This process was repeated 5 times and each time, measuring the isolated yields exactly confirmed that the catalytic efficiency of the catalyst was not changed and nanoparticles were not deactivated during catalysis the reactions (Scheme 2).

((Scheme 3))

To verify that the size and morphology of the nanoparticles were not changed during the process, the SEM images of the recovered nanoparticles were obtained after second (Scheme 3-a) and fifth (Scheme 3-b) runs. According to these images, any significant alteration was not observed and size, morphology and dispersity of the NPs remained unchanged. Also, the leaching of the catalyst was examined. To this end, the reaction between bromobenzene and phenylacetylene was repeated simultaneously in two different vessels under the optimized reaction conditions. In each case, the reaction progress was monitored using GC after 20 minutes. Then the catalyst's nanoparticles were collected from one of these vessels using a magnet, while the other was remained unchanged. Thereafter, both of the reactions were continued under the same conditions. After another twenty minutes, both the reactions were stopped and their completion was again examined using GC. The results showed that the reaction in the absence of the catalyst was not proceeded any more, while the progress of the reaction in the other vessel was considerable. This observation confirmed that leaching was not occurred in the reaction medium during the process. So, the proposed catalytic system not only can catalyze appropriately the Sonogashira reaction of aryl- and alkyl halides, both also can be reused for several times without any significant activity lost.

((Scheme 4))

On the other hand, it is found previously that the presence of metal contaminants presented in the iron source can catalyze these reactions [34, 35]. So, in order to verify that this phenomenon does not affect the reaction, a control experiment was done using 10 mol% of $FeCl_3$ as catalyst under the optimized reaction conditions. The reaction of phenyl acetylene with bromobenzene and also 4-bromoanisole was selected as model reactions. Having comparable results with those in the presence of nickel ferrite, the reaction of bromobenzene and of 4-bromoanisole were stopped after 1 and 3 hours, respectively. In both cases, the reactions show no progress using $FeCl_3$ as catalyst. When let the reactions to stir and heat for 24 hours, a time much longer than the required time for completion of the reactions performed using nickel ferrite, a small amounts of the corresponding products were formed, but in negligible amounts as can be seen in scheme 4.

((Scheme 5))

Another control experiment was done using $NiCl_2$ as catalyst to confirm the absence of metal contaminants in the nickel source. To this end, the reaction between 4-bromoanisole and phenyl acetylene was repeated under the optimized reaction conditions using 10 mol% of $NiCl_2$ as catalyst. Again, the reaction was stopped after 3 hours and its conversion and yield were determined exactly. The amount of the desired product in this case was also very small (Scheme 5).

((Scheme 6))

To carry out the Hg poisoning test, Hg (Hg: $NiFe_2O_4$; 400: 1) was put in a reaction flask. Thereafter, 4-bromobenzaldehyde (1.0 mmol), phenyl acetylene (1.0 mmol) and the requisite amount of catalyst nanoparticles were added to it. The reaction was carried out under optimum conditions. The progress of the reaction was monitored with TLC. After continuing the reaction further for 2.5 h at 100 °C, only a 42% yield could be reached.

1.4 Conclusion

Summarily, superparamagnetic nickel ferrite nanoparticles were employed in the Sonogashira reaction of various types of aryl- and alkyl halides in water. This catalyst is readily prepared from available starting materials and also is a reusable catalyst having very good stability to air, moisture and elevated temperatures. The proposed procedure applied here for the Sonogashira reaction leads to better yields in approximately shorter times compared to previous reports using other catalytic systems. Therefore, considering these and its compliance with green chemistry principles, this methodology is a useful and general method for the coupling of terminal alkynes and aryl- or alkyl halides. In addition, because of total removal of the metal-based catalyst from the reaction media, the procedure can be applied in pharmaceutical and other sensitive synthetic procedures.

Acknowledgments

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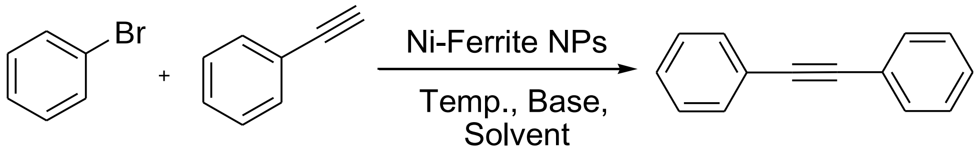
Table 1. Optimization of reaction conditions for Sonogashira reaction under conventional heating conditions[a]

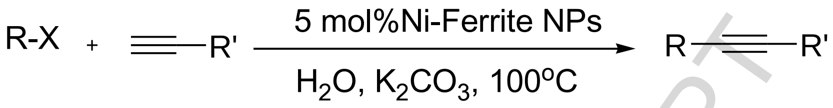


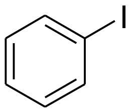
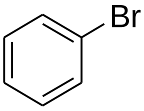
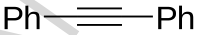
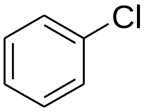
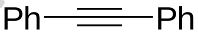
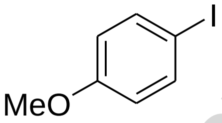
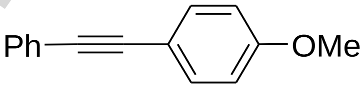
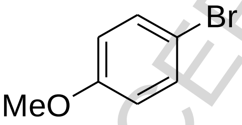
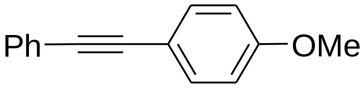
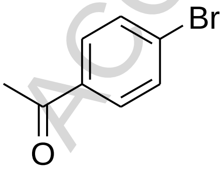
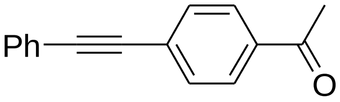
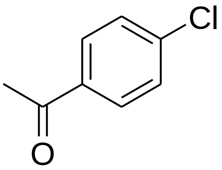
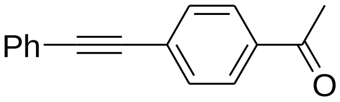
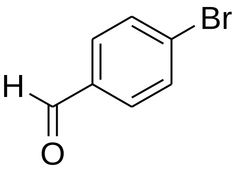
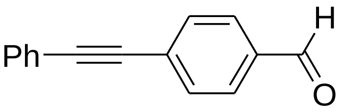
Entry	Solvent	Base	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)[b]
1	DMF	K_2CO_3	5	100	30	68
2	Toluene	K_2CO_3	5	100	30	59
3	THF	K_2CO_3	5	reflux	30	54
4	$\mathbf{H_2O}$	$\mathbf{K_2CO_3}$	**5**	**reflux**	**30**	**72**
5	H_2O	Cs_2CO_3	5	reflux	30	73
6	H_2O	NaOAc	5	reflux	30	43
7	H_2O	NaOH	5	reflux	30	47
8	H_2O	Et_3N	5	reflux	30	51
9	H_2O	K_2CO_3	None	reflux	30	0
10	H_2O	K_2CO_3	0.1	reflux	30	20
11	H_2O	K_2CO_3	1	reflux	30	41
12	H_2O	K_2CO_3	2	reflux	30	53
13	H_2O	K_2CO_3	10	reflux	30	74
14	H_2O	K_2CO_3	5	60	30	62
15	H_2O	K_2CO_3	5	r.t.	30	40

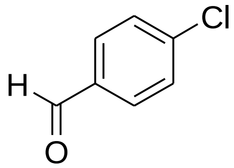
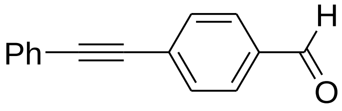
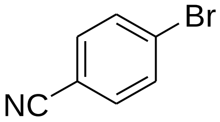
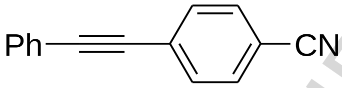
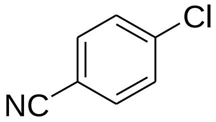
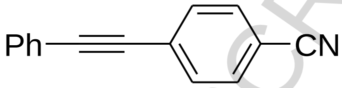
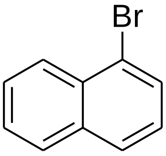
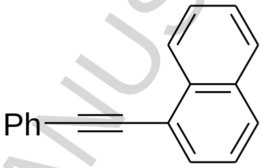
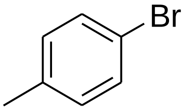
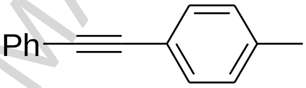
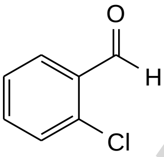
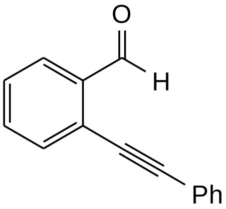
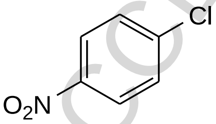
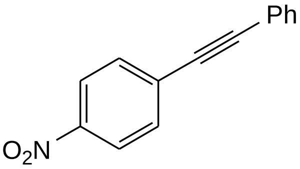
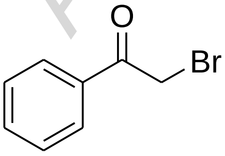
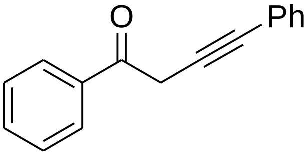
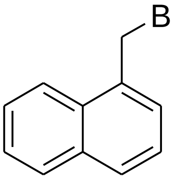
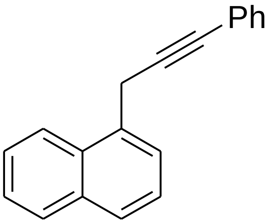
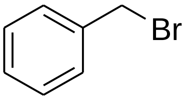
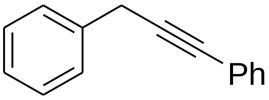
[a] Reaction condition: bromobenzene (1 mmol), phenyl acetylene (1 mmol), Base (1.1 mmol), catalyst, Solvent (3 ml) and Temperature.

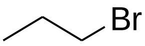
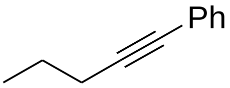
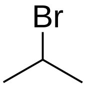
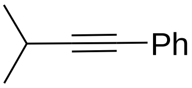
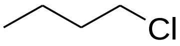
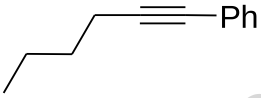
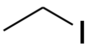
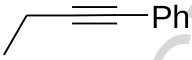
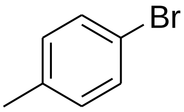
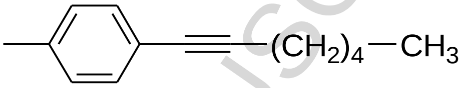
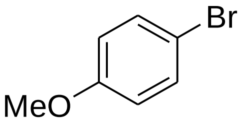
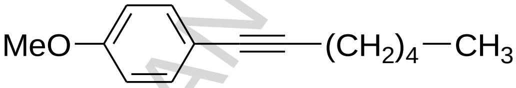
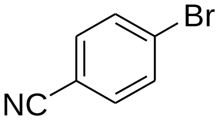
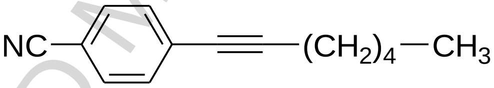
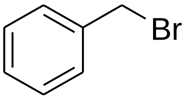
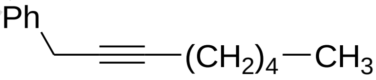
[b] Isolated yield

Table 2. The Sonogashira reaction of various aryl halides under optimized reaction conditions[a]



Entry	RX	Product	Time (h)	Yield (%)[b]
1			0.75	95
2			1	94
3			1.5	92
4			2.5	93
5			3	91
6			2	89
7			2.5	90
8			2.5	91

9			3	92
10			2	88
11			2.25	85
12			2	89
13			2	90
14			4	87
15			2	93
16			3	86
17			2	85
18			1.5	88

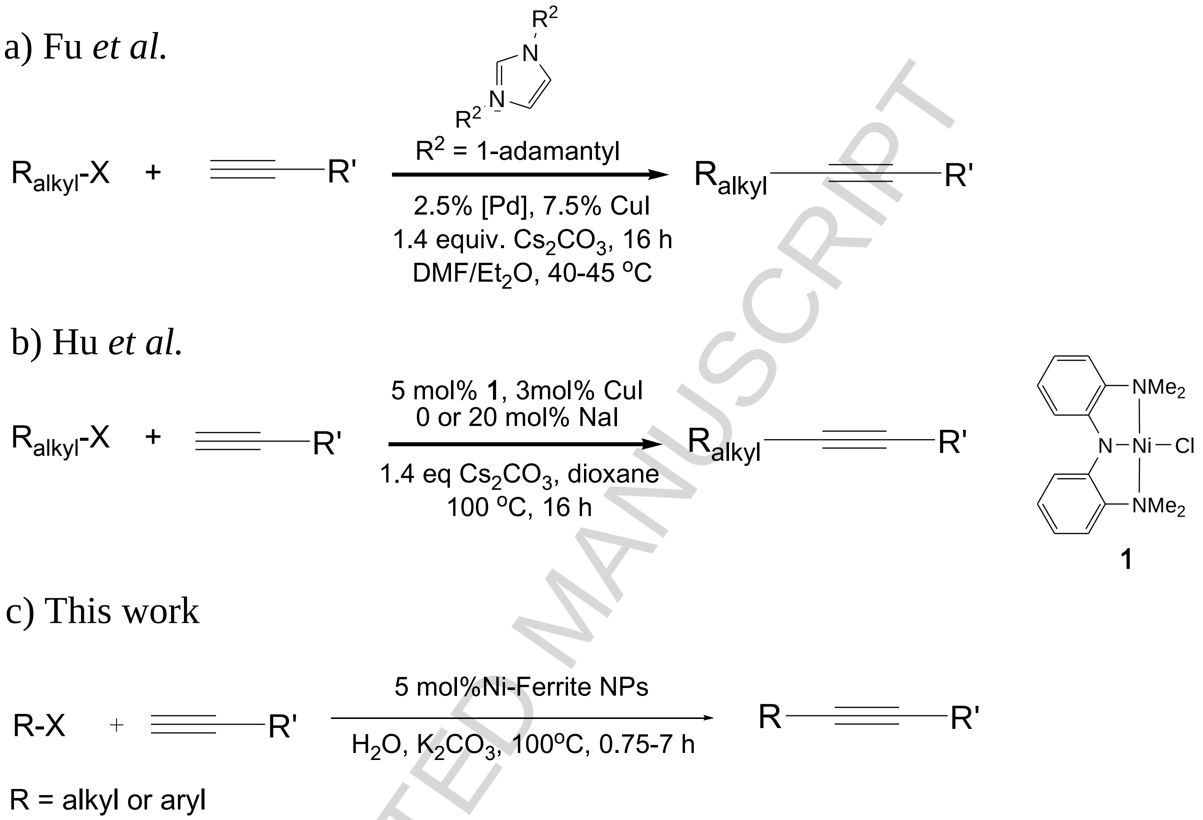
19			6	78
20			7	73
21			7	70
22			5	80
23			2.5	83
24			3	84
25			2.25	87
26			2.5	81

[a] Reaction condition: aryl/ alkyl halide (1 mmol), alkyne* (1 mmol), K_2CO_3 (1.1 mmol), catalyst (5 mol%), H_2O (3 ml) and 100 ^oC.

[b] Isolated yield.

*alkyne = phenyl acetylene or 1-heptyne

((Scheme 1))



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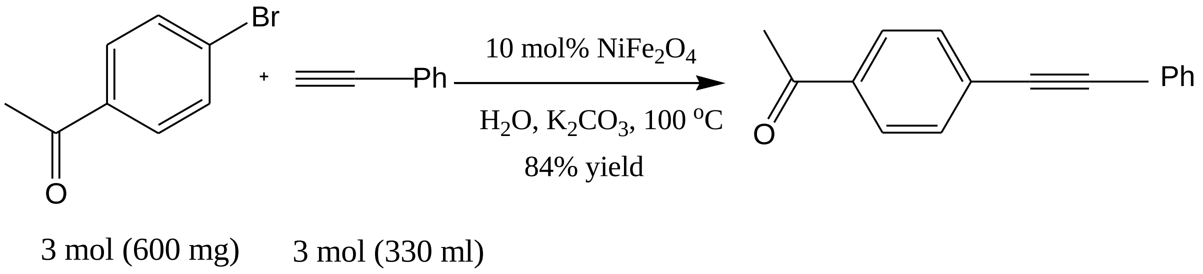

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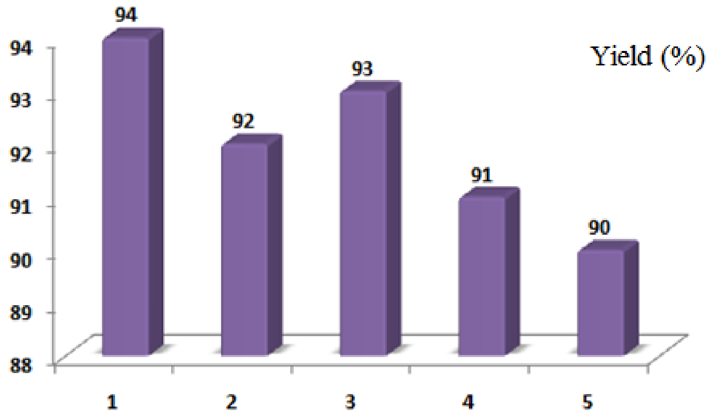

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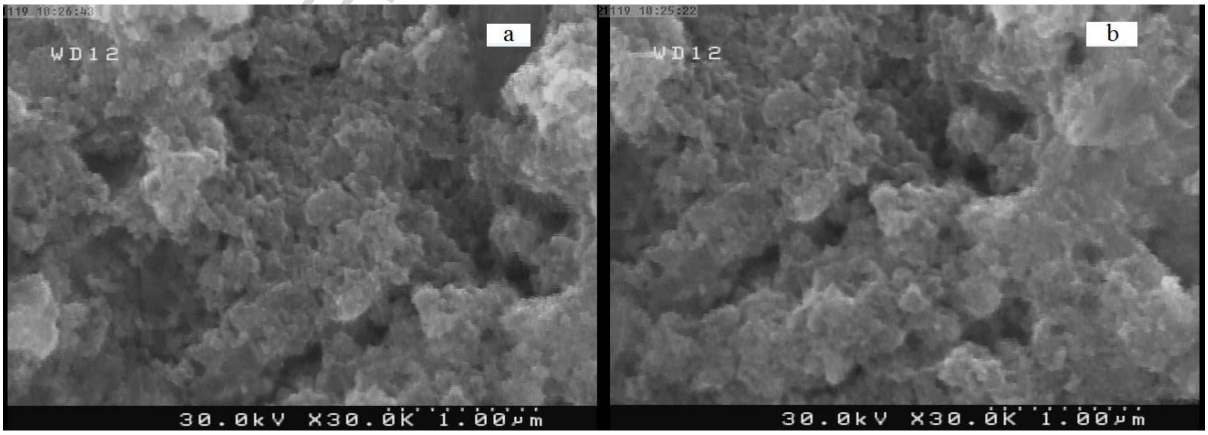

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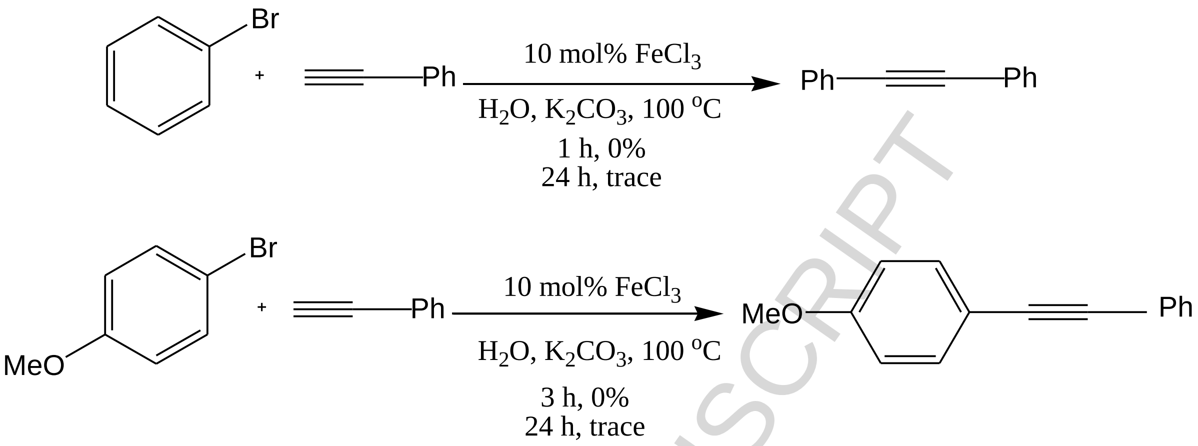

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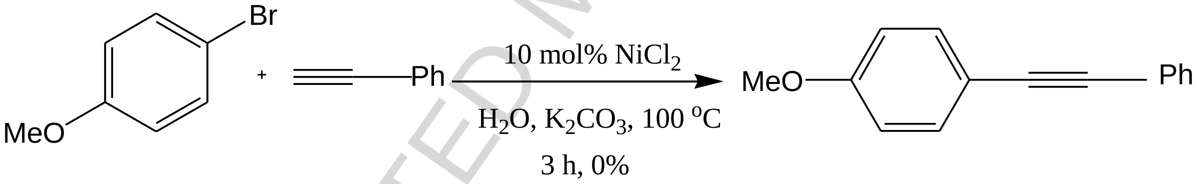


Legends

Scheme 1. Comparison of the previous C_{sp}-alkyl halide Snogashira couplings with present work [30, 31]

Scheme 2. Sonogashira reaction in large scale.

Scheme 3. Recovery and reuse of nickel ferrite nanoparticles for the Sonogashira reaction. Reaction conditions: bromobenzene (1 mmol), phenyl acetylene (1 equiv.), nano nickel ferrite (5 mol %), K_2CO_3 (1.1 mmol), water (3 ml) and reaction stirred at 100 °C.

Scheme 4. SEM pattern of recovered nickel ferrite nanoparticles after second (a) and fifth (b) runs of the Sonogashira reaction

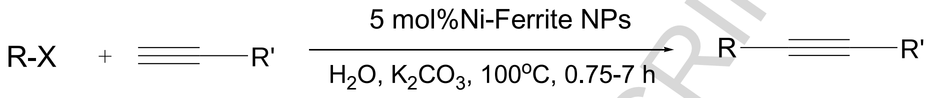
Scheme 5. Investigation of the probability of catalytic activity of metal contaminants presented in iron source. a) Reaction of bromobenzene with phenyl acetylene in the presence of 10 mol% of $FeCl_3$ under optimized conditions; b) Reaction of 4-bromoanisole with phenyl acetylene in the presence of 10 mol% of $FeCl_3$ under optimized reaction conditions.

Scheme 6. Investigation of the probability of catalytic activity of metal contaminants presented in nickel source: Reaction of 4-bromoanisole with phenyl acetylene in the presence of 10 mol% of $NiCl_2$ under optimized reaction conditions.

Graphical abstract

A copper-free Sonogashira reaction using nickel ferrite as catalyst in water

Firouz Matloubi Moghaddam, Ghazal Tavakoli and Hamid Reza Rezvani



R = alkyl or aryl

R' = Ph or C_5H_{11}

X = I, Br, Cl

Highlights

A copper-free Sonogashira reaction using nickel ferrite as catalyst in water

Firouz Matloubi Moghaddam, Ghazal Tavakoli and Hamid Reza Rezvani

- Nickel ferrite nanoparticles were applied successfully in Sonogashira reaction.
- Reactions were performed under green conditions using water as solvent.
- All the reactions were completed in short times with excellent yields.
- The magnetic catalyst can be separated easily using an external magnetic field.
- The catalyst is recyclable and reusable without activity lost.