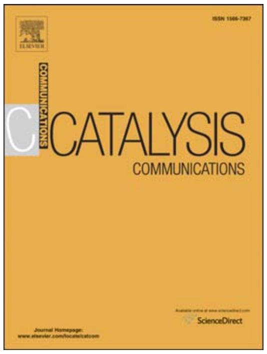

α-Arylation of oxindoles using recyclable metal oxide ferrite nanoparticles: Comparison between the catalytic activities of nickel, cobalt and copper ferrite nanoparticles

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α-Arylation of oxindoles using recyclable metal oxide ferrite nanoparticles: comparison between the catalytic activities of nickel, cobalt and copper ferrite nanoparticles

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Abstract

Three different spinel metal oxide catalytic systems including $NiFe_2O_4$, $CuFe_2O_4$ and $CoFe_2O_4$ were synthesized using co-precipitation technique and their catalytic activities were compared to each other in α-arylation of oxindole derivatives under the optimized reaction conditions. Both nickel ferrite and copper ferrite magnetic nanoparticles show approximately the same behaviour in these reactions but cobalt ferrite ones indicate slightly different properties and were not as good as the other two catalysts. These superparamagnetic catalysts allowed that α-arylation of different types of oxindoles to be occurred in high yields under mild conditions and at very short times.

Keywords: oxindole • α-arylation • superparamagnetic nanoparticles • recyclable catalyst • heterogeneous catalysis

Introduction

One of the important structures that can be found most frequently in many natural products, pharmaceutical targets and biologically active molecules is oxindole and its derivatives [1,2]. These compounds exhibit antiabacterial and antifungal activities [3]. These C-3 functionalized oxindoles can be used as drugs against a variety of neurodegenerative disorders [5] and also show anti-tumor [6] and anti-HIV properties [7]. One of the most important oxindoles are C-3 aryl ones playing a significant role in some biological routes [2,4]. A number of techniques have been reported for synthesizing C-3 functionalized derivatives of oxindoles, especially C-3 arylated ones [4,8-14]

Metal-catalyzed routes for this purpose are of most important and efficient methods. Previously reported methodologies based on classical chemical reactions [4,15-20] do not work when the substrate contained the oxindole core. In such cases, intermolecular arylation of the C-3 position of oxindole in the presence of a metal-based catalyst is what required, something named as metal-catalyzed α-arylation of carbonyl compounds [11-14]. Hartwig *et al*. in 2001 reported intramolecular α-arylation of oxindoles using Pd^0 as catalyst to give 3,3-disubstituted oxindoles (Scheme 1a) [4]. In 2008, Durbin and Willis synthesized α-arylated oxindoles using $Pd(dba)_2$ as catalyst (Scheme 1b). Walsh *et al*. in 2013 reported α-arylation of acetamides with aryl chlorides in the presence of a palladium precatalyst and a phosphinic ligand (Scheme 1c) [21]. Application of a strong base is necessary in all these report to deprotonate the amidic α-proton. These works uses palladium with phosphine ligands that suffers from some drawbacks. For example, palladium is a high cost, toxic and moisture-sensitive transition metal that often needs to certain types of ligands, especially phosphinic ones, to be active and effective [22]. The catalytic systems employed by Walsh and also by Durbin and Willis are both homogeneous and none of them are recyclable. On the other hand, application of ligands in many organic reactions can be supposed as a source of limitation because many of these ligands are not available easily. These reactions are also performed under approximately harsh reaction conditions. There are some examples of α-arylation of carbonyl compounds using other transition-metal based catalysts, especially cuprous or cupric salts [23]. Application of such catalysts is also accompanied with some drawbacks. Cu(I) salts are also air-sensitive and require harsh conditions to be kept stable. Furthermore, these metal sources may contaminate the final products leading to limitations on their usage as drugs.

((Scheme 1))

On the other hand, among the carbonyl containing compounds, α-arylation of amide enolates is most challenging due to high pK_a values of the substrates [14]. As far as we know, there is a few reports regarding metal-catalyzed C-3 arylation of oxindoles [24]; so, introducing new efficient methodologies to this end could be of high importance. Due to the limitations of previous catalytic systems, there remains a need for introducing low-cost and readily available catalysts with high efficiency. Magnetic metal oxide nanoparticles, especially those with spinel structure, have attracted many attentions recently. In fact, the presence of two transition metals in these systems could enhance their catalytic activity because of the synergistic effect between the two metals [25,26]. These heterogeneous catalysts not only have considerable catalytic activity, but also can be synthesized easily. In addition, they can be recovered simply from the reaction media using an external magnetic field and can be reused for several times. This is the main advantages of these systems especially from the industrial view point [27-29].

Considering all these facts and many others, we decided to employ superparamagnetic nickel ferrite nanoparticles as catalyst in the α-aryaltion of oxindoles. These spinel nanoparticles were synthesized and characterized previously by our group and their excellent catalytic activity in various C-C and C-heteroatom coupling reactions was demonstrated [30,31]. Herein, in continuation of our previous works, the applicability of these magnetic nanoparticles as an efficient catalytic system in α-arylation of oxindoles is reported. Different types of oxindole derivatives having substituents on the aromatic ring or without that were synthesized and used as substrate in this reaction. Results show that compared to the previously reported Pd- or Cu-catalyzed α-arylation reactions [14,24,32], this procedure could functionalized C-3 position of oxindoles successfully with very good yields in reasonably shorter reaction times. These remarkable results encouraged us to do a comparative investigation to find a catalyst with best catalytic behavior for this reaction. To this end, two additional metal oxides, *i.e.* copper ferrite and cobalt ferrite nanoparticles were synthesized [30] and their activity as catalyst was examined in the α-aryalation of oxindoles under the same reaction conditions.

Results and Discussion

Nickel, cobalt and copper ferrite magnetic nanoparticles were synthesized using co-precipitation method[30]. These nanoparticles were used as catalyst in the α-arylation reaction of oxindole derivatives and their activities were compared to each other.

Optimum reaction conditions were determined initially using nickel ferrite nanoparticles as catalyst. The reaction between *N*-methyl oxindole and bromobenzene was selected as the model reaction and the effect of each of the parameters on this reaction was considered carefully (Table 1). The reaction resulted in the formation of two products, **1a** and **1b**, depends on the reactant ratios and other conditions.

As can be seen in table 1, when the reaction is conducted in DMSO, Toluene and NMP, the formation of byproduct **1b** is unavoidable. The model reaction also was performed in H_2O as the green solvent but its yield was not good. Finally, using 1,4-dioxane as solvent, not only yield of the reaction was much better, but also the ratio of products **1a** to **1b** is very high and it can be said that the reaction approximately resulted in the selective formation of **1a** as the sole product (Table 1, entry 4).

The effect of various organic and inorganic bases also was investigated (Table 1, entries 4, 6-9). Both K_2CO_3 and KO*t*-Bu resulted in full conversion of the substrate under these reaction conditions; however, using KO*t*-Bu as base, higher amount of byproduct, **1b**, is produced in the reaction (Table 1, entry 8). Therefore, K_2CO_3 was selected as the best base (Table 1, entry 4).

((Table 1))

In order to optimize the amount of catalyst required for such transformation, the model reaction was repeated in the absence of catalyst and also in the presence of 1, 2, 5 and 10 mol% of $NiFe_2O_4$ nanaoparticles (Table 1, entries 4, 10-13). As it is shown in table 1, the reaction does not progress in the absence of catalyst. In addition, when 1 or 2 mol% of nickel ferrite nanoparticles were used, reaction rate is not so high and their yields are moderate; however, when the catalyst concentration increases to 5 mol%, very good yield could be obtained in a reasonable time and with minimum formation of the byproduct (Table 1, entry 13). Further increase in the amount of catalyst (up to 10 mol%) does not give rise to higher reaction rate and better yields of **1a**.

Conducting the model reaction at 100 ^{o}C, 70 ^{o}C , 45 ^{o}C and also at room temperature (Table 1, entries 13-16) showed that although the reaction rate and conversion is relatively low at 45 ^{o}C and room temperature, the results obtained at 70 ^{o}C were excellent. At 100 ^{o}C, the reaction rate was not increased but higher amount of **1b** was formed.

In the final step, reactant ratio was investigated. Results indicated that decreasing the amount of bromobenzene to 1 equivalent caused the formation of **1a** as the sole product (Table 1, entry 17).

Having these reaction conditions in hand, scope of the reaction between different types of aryl halides and oxindole derivatives was explored (Table 2). As can be seen, the reaction has very good functional group tolerability and all types of aryl halides containing various substituents on the phenyl ring can be used in this reaction. Furthermore, not only aryl iodides and bromides but also the less reactive aryl chlorides could be used effectively under the defined conditions. In all cases, the reactions were completed in reasonably short times under relatively mild conditions and with very good to excellent yields. In addition, all the reactions show very good selectivity for the monoarylated oxindole derivatives. Comparison of 4-chloroacetophenone and 2-chloroacetophenone reveals that the 2-substituted one required longer reaction time to be completed; it can be attributed to more steric hindrance around the active site of the reaction (*i.e.* Cl) in the later case.

((Table 2))

On the other hand, the scope of the reaction regarding oxindole was also investigated (Table 2). Different derivatives of oxindoles including *N*-methyl, ethyl, phenyl and benzyl oxindoles and also 5-methoxy-*N*-benzyl and 5-methyl-*N*-methyloxindole were synthesized [33] and used in the reaction. Again, all the reactions were completed in very short times with excellent yields.

Observing such good results encouraged us to test the reaction using other metal oxide nanoparticles and compared their catalytic activities with $NiFe_2O_4$. So, we decided to investigate the activity of cobalt and copper ferrite nanopartcles in the α-arylation of oxindoles. To this end, magnetic nanoparticles of copper and cobalt ferrite were synthesized with the same procedure, characterized and were employed in the C3 functionalization of oxindoles. In order to have a fair comparison between these catalysts, all the reactions were carried out under the optimized reaction conditions obtained using nickel ferrite nanoparticle as catalyst (Table 2).

According to the experiments, α-arylation reaction could be catalyzed efficiently using all these three catalytic systems. Yields and selectivities of $NiFe_2O_4$- and $CuFe_2O_4$ catalyzed reactions were comparable. Again, the nature of aryl group in the aryl halide moiety did not affect the results and the reactions did not show any sensitivity to the functional groups and substituents on the aromatic ring. However, when the reactions were carried out using cobalt ferrite nanoparticles, the probability for the formation of diarylated oxindoles increases and conversion of oxindoles to the desired products was not complete in some cases. The reactions also required longer reaction times to be completed. The situation was not observed so seriously in the case of copper ferrite.

The reusability of the cataysts in the reaction of bromobenzene with *N*-methyloxindole was investigated in the next step (supplementay data) (Figure 1). According to the obtained results, it can be said that the catalytic efficiency of both nickel and copper ferrite nanoparticles remains approximately constant during the course of the reactions. However, the catalytic activity of $CoFe_2O_4$ is decreased after the 5th run.

((Figure 1))

It is demonstrated that the presence of metal contaminants presented in the iron source can catalyze the coupling reaction between aryl halides and various types of nucleuphiles [34,35]. So, a control experiment was done using 5 mol% of $FeCl_3.6H_2O$ as catalyst (Scheme 2). The result showed that $FeCl_3.6H_2O$ is unable to catalyzed the reaction effectively.

((Scheme 2))

Conclusions

In Summary, α-arylation of different oxindole derivatives was examined using magnetic metal oxide nanoparticles as catalyst. Three different catalytic systems including $NiFe_2O_4$, $CuFe_2O_4$ and $CoFe_2O_4$ were synthesized and characterized and their application in the C3-arylation of oxindoles was investigated. Also, the catalytic activity, reusability and leaching phenomenon of these catalysts were compared to each other. Both nickel ferrite and copper ferrite nanoparticles show approximately the same behavior in these reactions but $CoFe_2O_4$ indicate slightly different properties and were not as good as the two other catalysts. The rate of precipitation and also the reusability of the nickel and copper ferrite nanoparticles were higher than cobalt ferrite. Leaching test's results showed that in contrast to most of heterogeneous catalysts, there is no leaching in these catalytic systems. In total, the three proposed catalytic systems have many advantages over the classic homo- and heterogeneous catalysts: they are synthesized easily from available and low-cost starting materials; they can be totally removed from the reaction media and finally, the exposure to air, moisture and elevated temperatures could not deactivate them.

The proposed conditions applied here lead to more convenient procedure compared to previous reports using other heterogeneous or homogeneous catalytic systems. Substitution pattern can be varied on both the oxindole and aryl halide and reactions showed no sensitivity toward electron-withdrawing or donating substituents on the reactants. All the reactions were completed in very short times with very good to excellent yields. Therefore, considering these mild conditions and the possibility for total removal of the metal-based catalyst from the reaction media, this methodology has enough potential to be used in pharmaceutical and other sensitive synthetic procedures.

Experimental Section

General Procedure for the α-arylation of oxindole derivatives

An oven-dried reflux tube equipped with a magnetic stir bar and a Teflon stopcock was charged with aryl halide (1 mmol), oxindole (1 mmol), potassium carbonate (1.1 mmol), catalyst nanoparticles (0.05 mmol) and 1,4-dioxane (2 ml) and heated at 70 ^{o}C. The mixture was vigorously stirred under these reaction conditions and completion of the reaction was monitored by TLC (EtOAc: *n*-hexane, 25:75).

After completion of the reaction, the reaction mixture was cooled to room temperature, the magnetic nanoparticles of the catalyst were collected using a megnet. Ethyl acetate (5 mL) and water (10 mL) were added to the mixture in the next step. The aqueous layer was further extracted by ethyl acetate (2*5 mL). The combined organic layers were washed with saturated brine, dried over $CaCl_2$, filtered, and concentrated to give a residue which was purified by recrystallization from ethanol and water or by column chromatography on silica gel using EtOAc: *n*-hexane, 1:7.

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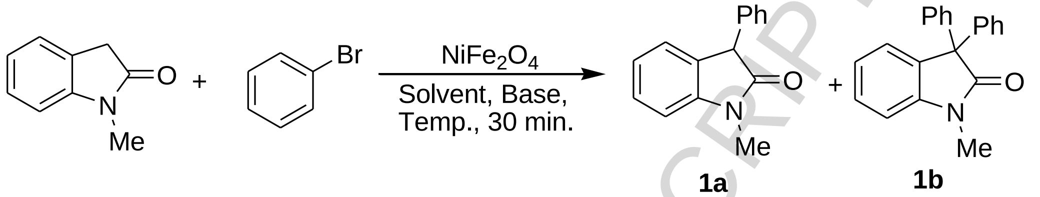
((List of Tables))

Table 1. Screening the reaction conditions for α-arylation of oxindole derivatives.[a]



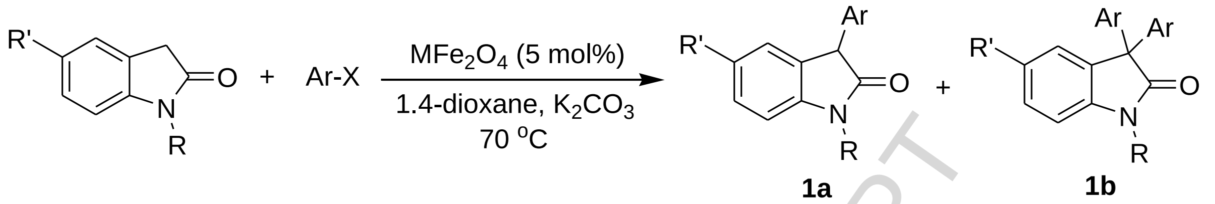
Entry	Solvent	Base	Catalyst (mol%)	Temperature (^oC)	Yield (%)[b]	
					1a	1b
1	DMSO	K_2CO_3	10	100	62	14
2	Toluene	K_2CO_3	10	100	53	11
3	H_2O	K_2CO_3	10	100	44	6
4	1,4-dioxane	K_2CO_3	10	100	86	7
5	NMP	K_2CO_3	10	100	66	13
6	1,4-dioxane	Cs_2CO_3	10	100	71	8
7	1,4-dioxane	NaOAc	10	100	45	11
8	1,4-dioxane	KO^tBu	10	100	82	12
9	1,4-dioxane	Et_3N	10	100	64	10
10	1,4-dioxane	K_2CO_3	None	100	Trace	0
11	1,4-dioxane	K_2CO_3	1	100	43	Trace
12	1,4-dioxane	K_2CO_3	2	100	61	3
13	1,4-dioxane	K_2CO_3	5	100	85	6
14	1,4-dioxane	K_2CO_3	5	70	86	4
15	1,4-dioxane	K_2CO_3	5	45	52	0
16	1,4-dioxane	K_2CO_3	5	RT	43	0
17[c]	1,4-dioxane	K_2CO_3	5	70	85	0

[a] Reaction conditions: *N*-methyl oxindole (1 mmol), Bromobenzene (1.2 mmol), Base (1.1 mmol), Catalyst, Solvent (2 mL), Temperature (^oC).

[b] Isolated yield.

[c] *N*-Methyl oxindole (1 mmol), Bromobenzene (1 mmol).

Table 2. α-Arylation of oxindole derivatives under optimized conditions.[a]



Entry	ArX	R	R'	Yeild (%)[b,c,d]			Time (min)		
				NiFe$_2$O$_4$	CoFe$_2$O$_4$	CuFe$_2$O$_4$	NiFe$_2$O$_4$	CoFe$_2$O$_4$	CuFe$_2$O$_4$
1	Iodobenzene	Me	H	95: ND[e]	93: ND	95: ND	60	90	50
2	Bromobenzene	Me	H	95: ND	94: ND	94: ND	60	90	60
3	Chlorobenzene	Me	H	94: ND	92: ND	93: ND	80	120	90
4	4-Bromotoluene	Me	H	92: Trace	90: Trace	93: Trace	90	150	100
5	4-Bromoanisole	Me	H	91: Trace	90: 4	93: Trace	90	180	90
6	4-Bromobenzonitrile	Me	H	92: Trace	88: 5	91: Trace	100	180	90
7	4-Chlorobenzaldehyde	Me	H	90: Trace	85: 5	89: Trace	150	240	180
8	4-Chloroacetophenone	Me	H	91: Trace	87: Trace	91: Trace	180	300	200
9	2-Chloroacetophenone	Me	H	85: ND	81: Trace	87: Trace	180	330	180
10	1-Bromonaphthalene	Me	H	95: ND	93: Trace	95: ND	120	270	100
11	Chlorobenzene	Et	H	94: ND	95: Trace	95: ND	80	150	80
12	4-Bromoanisole	Et	H	92: ND	87: 7	91: ND	80	150	90
13	4-Bromobenzonitrile	Et	H	93: Trace	90: Trace	91: Trace	90	180	100
14	4-Chloroacetophenone	Et	H	90: Trace	84: 10	89: Trace	150	300	180
15	Chlorobenzene	Ph	H	93: Trace	91: 8	95: ND	90	240	80
16	4-Bromoanisole	Ph	H	90: ND	85: 5	91: ND	120	300	120
17	4-Bromobenzonitrile	Ph	H	93: ND	88: 7	92: ND	100	300	120
18	4-Chloroacetophenone	Ph	H	91: Trace	87: 6	90: ND	100	360	90
19	Chlorobenzene	CH$_2$Ph	H	95: Trace	91:5	94: ND	90	150	100
20	4-Bromoanisole	CH$_2$Ph	H	92: Trace	89: 7	92: ND	120	180	140
21	4-Bromobenzonitrile	CH$_2$Ph	H	90: ND	87: 5	91: ND	120	240	120
22	2-Chloroacetophenone	CH$_2$Ph	H	88: Trace	88: Trace	90: ND	180	360	200
23	Chlorobenzene	CH$_2$Ph	OMe	90: ND	90: 7	91: Trace	90	180	80
24	4-Bromoanisole	CH$_2$Ph	OMe	89: ND	90: 5	90: 5	120	180	140
25	4- Chloroacetophenone	CH$_2$Ph	OMe	92: ND	90: 9	91: ND	120	240	120
26	2-Chloroacetophenone	CH$_2$Ph	OMe	87: ND	84: 5	85: Trace	240	420	270
27	1-Bromonaphthalene	CH$_2$Ph	OMe	92: ND	90: Trace	93: ND	80	180	90
28	Chlorobenzene	Me	Me	95: Trace	89: 8	94: Trace	80	150	80
29	4-Bromoanisole	Me	Me	93: Trace	90: 7	93: ND	100	240	120

30	4- Chloroacetophenone	Me	Me	91: ND	90: 5	92: ND	90	180	80
31	2- Chloroacetophenone	Me	Me	86: ND	82: 6	88: ND	180	420	240

[a] Reaction conditions: aryl halide (1 mmol), oxindole (1 mmol), K_2CO_3 (1.1 mmol), catalyst (5 mol%), 1,4-dioxane (2 ml) and 70 ^oC.

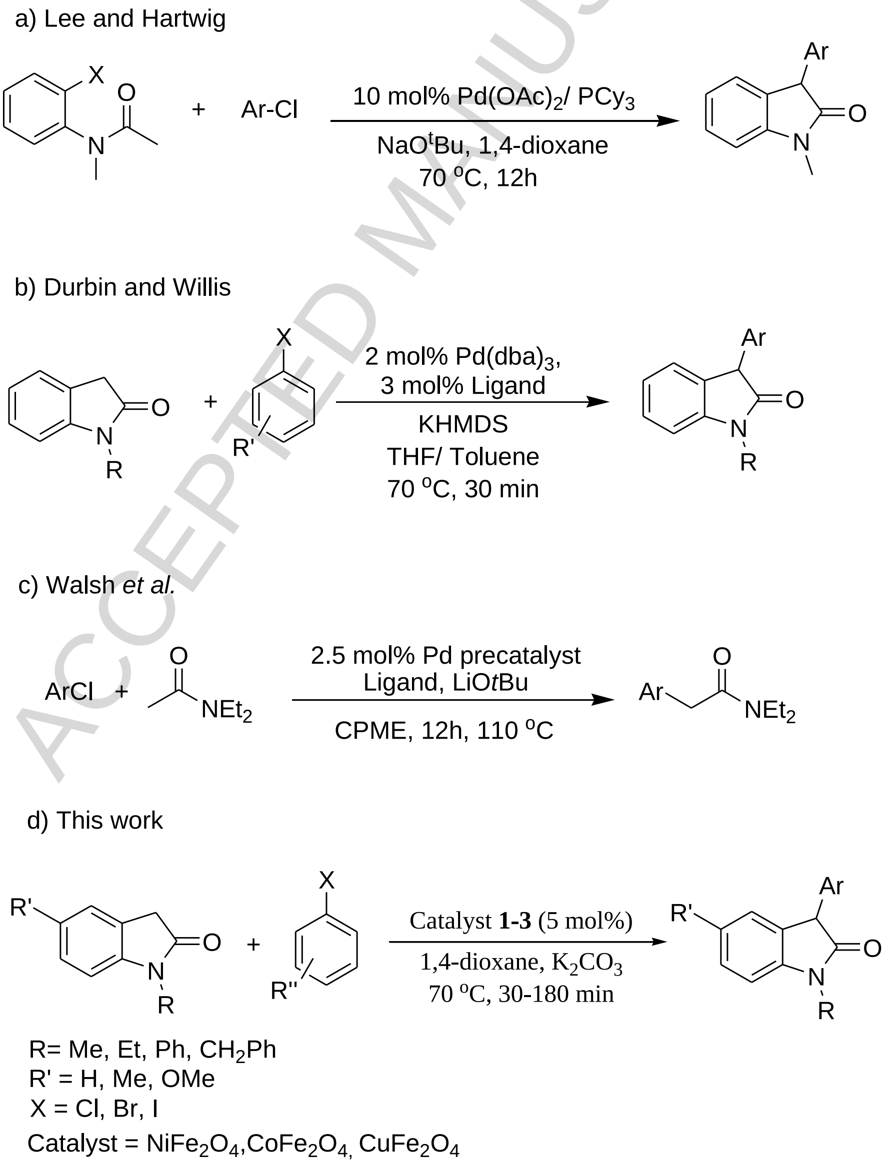
[b] All reactions have enough time to be completed with full conversions with respect to oxindoles.

[c] Isolated yield.

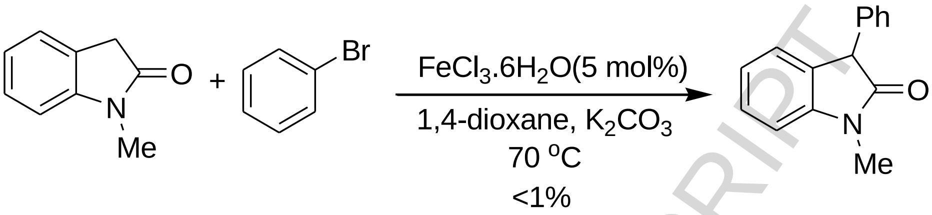
[d] **1a:1b** ratio.

[e] Not detected.

List of Schemes and Figures



Scheme 1. Comparison of previous reports on α-aryaltion of oxindoles with this work.



Scheme 2. Control experiment for confirming the essential role of metal ferrite nanoparticles as catalyst.

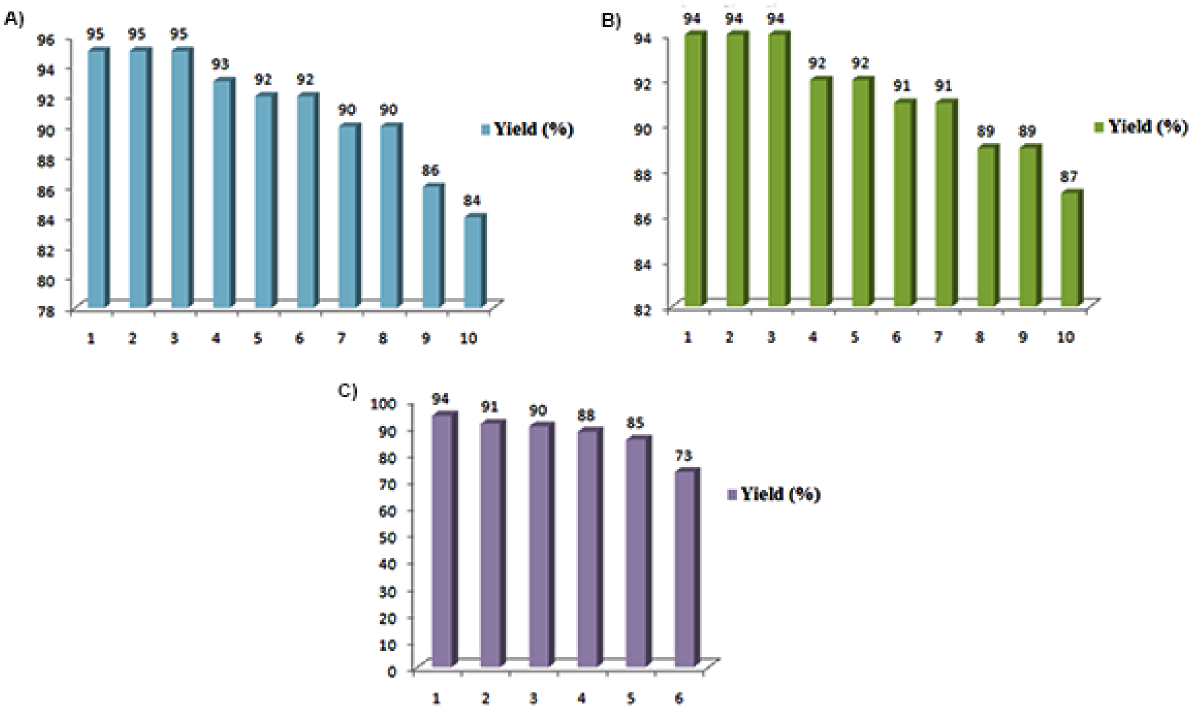


Figure 1. Recovery and reuse of a) nickel ferrite nanoparticles; b) copper ferrite nanoparticles; and c) cobalt ferrite nanoparticles in the α-arylation reaction of bromobenzene and *N*-methyl oxindole; Reaction conditions: bromobenzene (1 mmol), oxindole (1 mmol), catalyst (5 mol %), K_2CO_3 (1.1 mmol), 1,4-dioxane (2 mL) and 70 °C.