Magnetic Copper Ferrite Nanoparticles: An Inexpensive, Efficient, Recyclable Catalyst for the Synthesis of Substituted Benzoxazoles via Ullmann-Type Coupling under Ligand-Free Conditions

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Abstract: A new sustainable strategy for the synthesis of benzoxazoles from substituted *N*-(2-halophenyl)benzamides was developed in which inexpensive, readily available, air-stable, recyclable copper(II) ferrite serves as a nanocatalyst. The nanocatalyst can be completely recovered with an external magnet and can be used seven times without significant loss of catalytic activity.

Key words: nanostructures, catalysts, copper, iron, heterocycles, cyclizations, coupling

Heterocycles occur widely in natural products, pharmaceuticals, dyes, organic materials, and bioactive molecules. As a result, the development of novel, efficient, and practical methods for the synthesis of heterocycles continues to stimulate an impressive number of research groups. Benzoxazole derivatives are an important subclass of heterocycles that occur widely in bioactive molecules. For example, they are found in a variety of natural products[1] and they are used as antimicrobial,[2] antibacterial,[3] and anticancer agents[4] and as fluorescent probes.[5] The synthesis of benzoxazoles has therefore received much attention. The classical method for the preparation of benzoxazoles involves condensation of 2-aminophenol[6] with a carboxylic acid in the presence of an acid, or with an aldehyde under oxidative conditions. Although these methods are useful, they have some drawbacks that limit their widespread use, such as lack of availability of appropriately substituted 2-aminophenols or the need to use harsh reaction conditions, for example, strong acids. Recently, Bolm[7] and Peng[8] and their respective co-workers attempted to convert 2-haloanilides directly into benzoxazoles; unfortunately, a high temperature (140 °C) or the use of a superbase system (KOH/DMSO) was required. These reactions might proceed by a benzyne-type mechanism, which can result in low selectivity. For example, *m*-iodoanilides as substrates can also be converted into benzoxazoles, even under the optimal reaction conditions.

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Transition-metal-catalyzed transformations are useful tools in synthetic organic chemistry.[9] They can provide some of the most attractive methods for synthesizing heterocyclic compounds from readily accessible starting materials under mild conditions. Recently, copper-catalyzed Ullmann-type C–X (X = N, O, S) bond formation has received significant attention and has provided a useful strategy for the synthesis of heterocycles.[10–12] Until now, benzoxazoles have been synthesized by using a copper salt-catalyzed C–O cross-coupling reactions.[13]

The reaction conditions, media, and catalysts used in the current chemistry are problematic from the standpoint of the principles of green chemistry.[14] The recovery of the catalyst after a catalytic reaction and its reuse without loss of activity remains a central idea of sustainable chemistry; furthermore, removal of any traces of metal catalyst from the end-product is essential, because the presence of metal contaminants is highly regulated, especially in the pharmaceutical industry. As a result, many recyclable supported catalytic systems have been developed.[15] For example, Kantam and co-workers reported an efficient method for the synthesis of benzoxazoles by using copper fluorapatite as a heterogeneous catalyst.[16] Punniyamurthy and co-workers exploited copper(II) oxide nanoparticles as efficient catalysts for C–N, C–O, and C–S cross-coupling reactions.[17] Excellent as these methods are, the small size of the particles involved often hampers their separation and recycling, and the efficiency of the recovered catalyst is somewhat reduced as a result of the filtration step, impeding the application of such methods on a large scale.

Recently, magnetic nanocatalysts have been shown to exhibit attractive catalytic activities in various reactions, in that they are easily prepared and inexpensive, have low toxicities and large surface-area-to-volume ratios, and can be easily separated by using an external magnetic force.[14] Inspired by the use of magnetically separable copper(II) ferrite ($CuFe_2O_4$) nanoparticles as a powerful catalyst for many organic transformations,[18] we examined the use of cheap, air-stable, recyclable copper(II) ferrite as a magnetically separable catalyst for the synthesis of substituted benzoxazoles by an Ullmann-type reaction under ligand-free conditions. To the best of our knowledge, this report

represents the first use of magnetic copper(II) ferrite nanoparticles for the synthesis of heterocycles by an Ullmann-type intramolecular C–O bond formation.

The copper(II) ferrite nanoparticles were prepared by the procedure described in the literature[18j] and were characterized by X-ray diffraction (Figure 1). The diffraction patterns of all the peaks matched closely those reported in the literature.[18d,e,j]

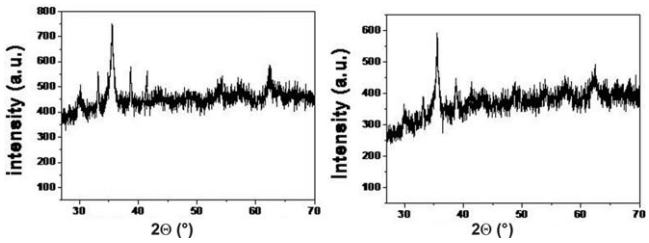


Figure 1 (a) X-ray diffraction spectrum of native copper(II) ferrite catalyst. (b) X-ray diffraction spectrum of reused copper(II) ferrite catalyst after the seventh cycle.

Scanning electron microscopy showed that the copper(II) ferrite nanoparticles remained in a similar state even after seven reaction cycles (Figure 2). Moreover, energy-dispersive x-ray spectroscopy showed that the spheres consisted of copper, iron, and oxygen, as expected (Figure 1, ESI$^+$).

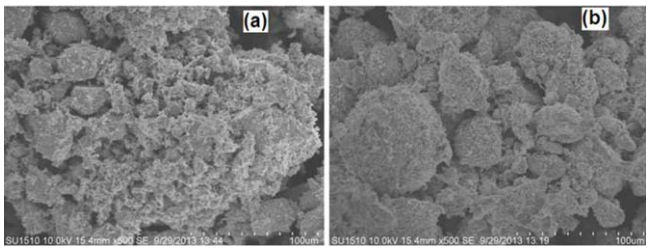
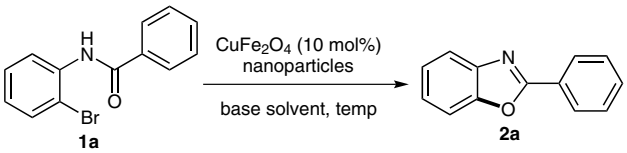


Figure 2 Scanning electron microscopy images of copper(II) ferrite nanoparticles before (a) and after (b) seven cycles of use

First, we used *N*-(2-bromophenyl)benzamide (**1a**) as a model substrates to optimize the reaction conditions, including the amounts of catalyst, the choice of base and solvent, and the reaction temperature under a nitrogen atmosphere (Table 1). First, we examined the effects of various solvents by using 0.1 equivalent of copper(II) ferrite nanoparticles as the catalyst and two equivalents of potassium carbonate as the base (relative to the amount of benzamide **1a**) (entries 1–4). Dimethyl sulfoxide gave the highest yield among the solvents tested (entry 2). We then examined the effect of the temperature (entries 5 and 6) and we found that 120 °C was optimal. Of the bases that we investigated, potassium carbonate was found to be most effective (entries 7–9). The yield fell when the amount of catalyst was reduced (entry 10). A control experiment confirmed that the desired heterocycle was not formed in the absence of the catalyst (entry 11).

Table 1 Optimization of Conditions for Magnetic Copper(II) Ferrite Catalyzed Cyclization of *N*-(2-Bromophenyl)benzamide (**1a**) to 2-Phenyl-1,3-benzoxazole (**2a**)

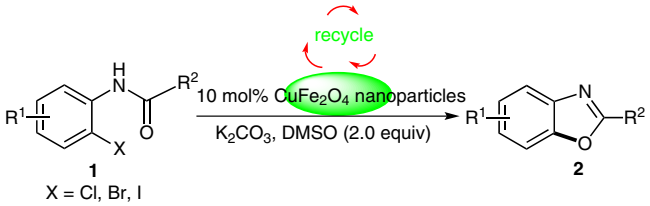


Entry[a]	Base	Solvent	Temp (°C)	Yield[b] (%)
1	K_2CO_3	DMF	120	90
2	**K_2CO_3**	**DMSO**	**120**	**96**
3	K_2CO_3	toluene	120	29
4	K_2CO_3	NMP	120	88
5	K_2CO_3	DMSO	90	35
6	K_2CO_3	DMSO	110	81
7	Cs_2CO_3	DMSO	120	76
8	K_3PO_4	DMSO	120	45
9	Na_2CO_3	DMSO	120	12
10[c]	K_2CO_3	DMSO	120	86[c]
11	K_2CO_3	DMSO	120	–[d]

[a] Reaction conditions: *N*-(2-bromophenyl)benzamide (**1a**; 0.5 mmol), catalyst (0.05 mmol), base (1.0 mmol), solvent (1 mL), N_2.
[b] Isolated yield.
[c] 0.025 mmol of catalyst was used.
[d] Not detected.

Next, we investigated the scope of the nanoparticle-catalyzed cyclization of substituted *N*-(2-halophenyl)benzamides (**1**) under the optimized conditions with 10 mol% copper(II) ferrite nanoparticles as the catalyst, two equivalents of potassium carbonate as the base (relative to the amide substrate), and dimethyl sulfoxide as the solvent at 120 °C under an atmosphere of nitrogen. The corresponding benzoxazoles (**2**) were obtained in good to excellent yields from a range of substrates at 90–120 °C (Table 2).[19] Among the substituted 2-haloanilides, 2-iodoanilides showed higher reactivities than the corresponding 2-bromoacetanilides, in that the intramolecular O-arylation of 2-iodoanilides occurred at 90 °C, whereas it was necessary to raise the temperature to 120 °C for 2-bromoanilides (entries 1, 4, 11, and 15). 2-Chloroanilides also showed moderate reactivities (entries 1, 2, 4, 8, 11, and 15). Compounds in which the benzoyl substituent R^2 was an electron-donating group showed higher reactivities than those in which it was an electron-withdrawing group. The magnetic copper(II) ferrite catalyzed reactions tolerated the presence of some functional groups such as trifluoromethyl (entries 4 and 11), chloro (entries 6 and 10), bromo (entries 5, 7, 8, and 9), or nitro (entry 15). Although the substrates containing aryl substituent R^2 showed high reactivity, unfortunately, aliphatic ones were pure substrates.

Table 2 Magnetic Copper(II) Ferrite Catalyzed Cyclization of Substituted *N*-(2-halophenyl)benzamides (**1**) to Substituted Benzoxazoles (**2**)



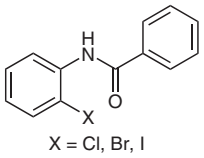
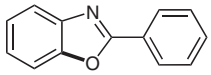
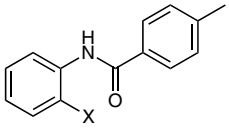
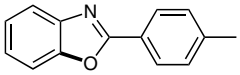
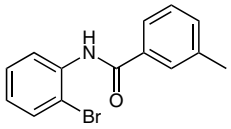
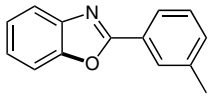
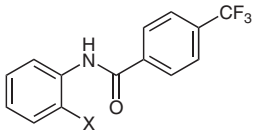
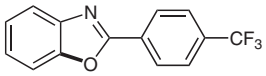
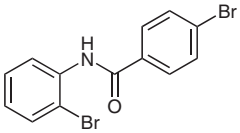
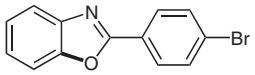
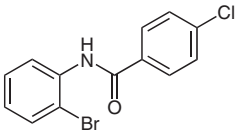
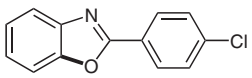
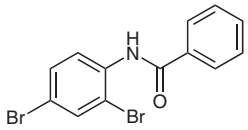
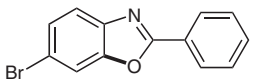
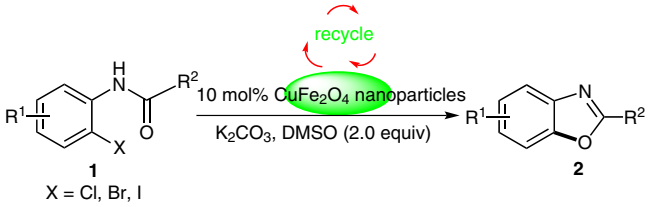
Entry	1	2	Yield[b] (%)
1	 X = Cl, Br, I **1a**	 **2a**	96; X = Br 95, 90[c]; X = I 67; X = Cl
2	 X = Cl, Br **1b**	 **2b**	99; X = Br 65; X = Cl
3	 **1c**	 **2c**	97
4	 X = Br, I **1d**	 **2d**	88; X = Br 94, 82[c]; X = I
5	 **1e**	 **2e**	95
6	 **1f**	 **2f**	93
7	 **1g**	 **2g**	93

Table 2 Magnetic Copper(II) Ferrite Catalyzed Cyclization of Substituted *N*-(2-halophenyl)benzamides (**1**) to Substituted Benzoxazoles (**2**) (continued)



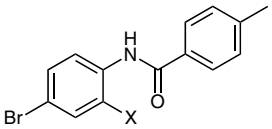
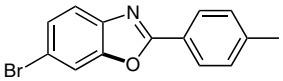
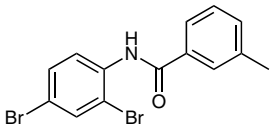
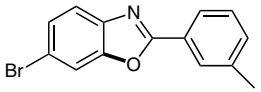
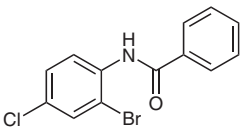
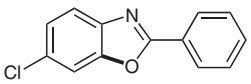
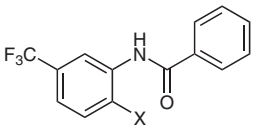
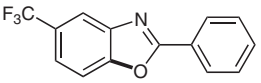
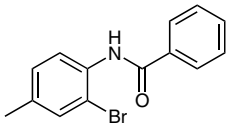
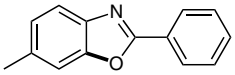
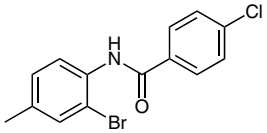
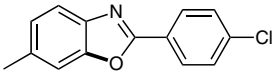
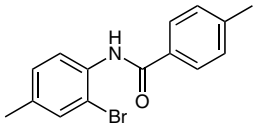
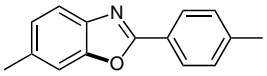
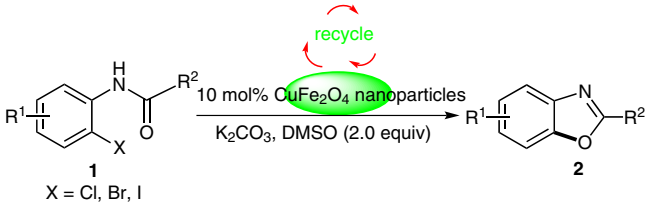
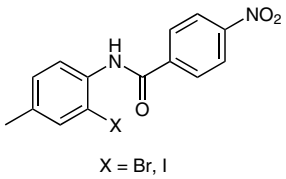
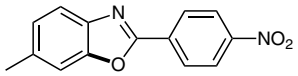
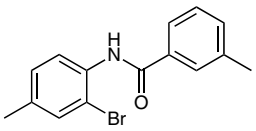
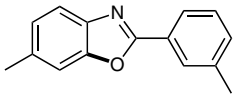
Entry	1	2	Yield[b] (%)
8	 X = Cl, Br **1h**	 **2h**	98; X = Br 61; X = Cl
9	 **1i**	 **2i**	94
10	 **1j**	 **2j**	95
11	 X = Br, I **1k**	 **2k**	85; X = Br 99, 90[c]; X = I
12	 **1l**	 **2l**	97
13	 **1m**	 **2m**	90
14	 **1n**	 **2n**	92

Table 2 Magnetic Copper(II) Ferrite Catalyzed Cyclization of Substituted *N*-(2-halophenyl)benzamides (**1**) to Substituted Benzoxazoles (**2**) (continued)



Entry	1	2	Yield[b] (%)
15	 X = Br, I **1o**	 **2o**	83; X = Br 96[c]; X = I
16	 **1p**	 **2p**	90

[a] Reaction conditions: *N*-(2-halophenyl)benzamide (**1**; 0.5 mmol), $CuFe_2O_4$ (0.05 mmol), K_2CO_3 (1.0 mmol), DMSO (1.5 mL), 120 °C, 24 h, under N_2.
[b] Isolated yield.
[c] 90 °C for 24 h.

We also studied the recyclability of the catalyst by examining the copper(II) ferrite catalyzed cyclization of *N*-(2-bromophenyl)benzamide under the optimized conditions (Figure 3). After completion of the reaction, the mixture was cooled to room temperature, and the catalyst was magnetically separated, washed with deionized water and diethyl ether, air dried, and then used directly for further catalytic reactions. The catalyst showed no significant loss of activity after seven cycles.

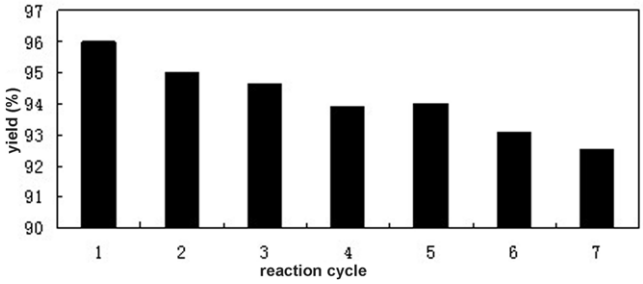
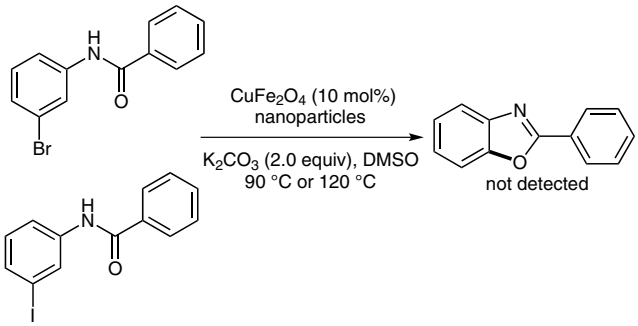


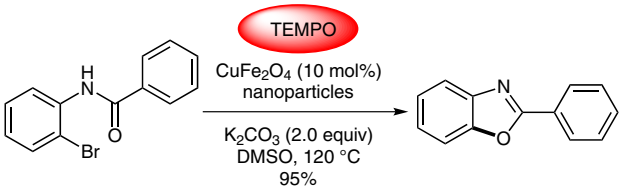
Figure 3 Yields from recycled copper(II) ferrite catalyst

Finally, we investigated the mechanism of formation of the benzoxazole derivatives. Reactions of *N*-(3-iodophenyl)benzamide or *N*-(3-bromophenyl)benzamide under the optimized reaction condition gave none of the cyclization product, indicating that the reaction does not proceed by a benzyne-type mechanism (Scheme 1).



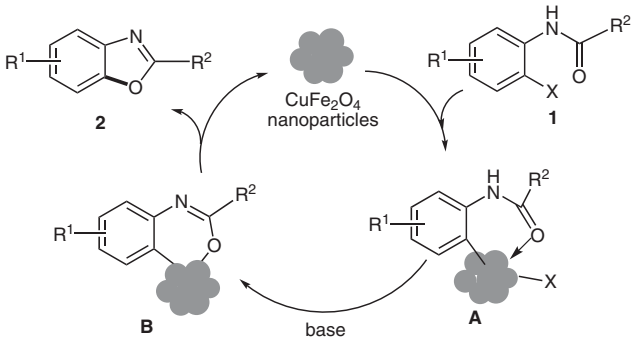
Scheme 1 Reactions of *N*-(3-iodophenyl)benzamide or *N*-(3-bromophenyl)benzamide under the optimized reaction conditions

Next, the reaction of benzamide **1a** was tested in the presence of one equivalent of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as a radical scavenger. No significant difference was observed in the yield (Scheme 2), ruling out the presence of radicals during the reaction.



Scheme 2 Reactions of *N*-(2-bromophenyl)benzamide in the presence of TEMPO under the optimized reaction conditions

On the basis of these results and reports in the literature,[13] we propose the mechanism shown in Scheme 3. Initially, copper(II) ferrite nanoparticles react with the substrate on their surface to generate intermediate **A**. This is then transformed into intermediate **B** in the presence of base, which completes the catalytic cycle by reductive elimination of the coupled product.



Scheme 3 Possible mechanism for copper(II) ferrite catalyzed synthesis of benzoxazoles

In conclusion, we have developed a simple and efficient magnetic copper ferrite nanoparticle-catalyzed method for the synthesis of substituted benzoxazoles by Ullmann-type coupling under ligand-free conditions. The protocol uses cheap, readily available, air-stable, recyclable copper(II) ferrite as the catalyst and substituted *N*-(2-halophenyl)benzamides as starting materials, and it gives the corresponding benzoxazoles in good to excellent yields under mild conditions. This method provides a new strategy for the synthesis of heterocycles. The strategy, which involves inexpensive, and efficient recyclable magnetic copper ferrite catalyst, will attract much attention in both academia and industry. Studies on further applications of copper(II) ferrite magnetic nanoparticles in the synthesis of heterocycles are in progress in our laboratory.

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(19) **2-Phenyl-1,3-benzoxazoles 2; General Procedure**

A 25 mL Schlenk tube equipped with a magnetic stirring bar was charged with $CuFe_2O_4$ nanoparticles (0.05 mmol, 12 mg), benzamide **1** (0.5 mmol), and K_2CO_3 (1.0 mmol, 139 mg). The tube was evacuated twice and backfilled with N_2. DMSO (1.5 mL) was added under N_2, the tube was sealed, and then the mixture was stirred at 90–120 °C for 24 h. When the reaction was complete, the solution was cooled to r.t. and concentrated in a rotary evaporator. The residue was purified by column chromatography (silica gel, PE–EtOAc).

2-Phenyl-1,3-benzoxazole (2a)

Eluent: PE–EtOAc (20:1); white solid; yield: 94 mg (96%); mp 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.6 Hz, 2 H), 7.80 (d, *J* = 3.2 Hz, 1 H), 7.61 (d, *J* = 3.6 Hz, 1 H), 7.62–7.54 (m, 3 H), 7.38 (d, *J* = 6.0 Hz, 2 H). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 163.1, 150.8, 142.1, 131.5, 128.9, 127.6, 127.2, 125.1, 124.6, 120.0, 110.6. ESI-MS: *m/z* = 196.3 $[M + H]^+$.

6-Chloro-2-phenyl-1,3-benzoxazole (2j)

Eluent: PE–EtOAc (20:1); white solid; yield: 109 mg (95%); mp 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 6.0 Hz, 2 H), 7.71–7.69 (d, *J* = 8.4 Hz, 1 H), 7.62–7.53 (m, 4 H), 7.36 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 163.7, 151.0, 141.0, 131.8, 130.7, 129.0, 127.7, 126.7, 125.3, 120.5, 111.3. ESI-MS: *m/z* = 230.5 $[M + H]^+$.