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### Copper Ferrite Superparamagnetic Nanoparticles as a Heterogeneous Catalyst for Directed Phenol/Formamide Coupling

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#### ARTICLE INFO

ABSTRACT

Article history:	The copper ferrite-catalyzed, directed coupling of ortho-arylated phenols and dialkylformamides		
Received	in the presence of a peroxide oxidant is described. Acyclic and cyclic amides were compatible with		
Received in revised form	the reaction conditions. The copper ferrite catalyst is heterogeneous since substantial leaching was		
Accepted	not detected and re-use of the catalyst for 9 consecutive reactions proceeded without a significant		
Available online	decrease in yield. To the best of our knowledge, this transformation has not been previously		
	performed under heterogeneous catalysis conditions.		
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copper ferrite			
C-H activation			
heterogeneous catalyst			
formamide			
phenol			

The formation of carbon-carbon and carbon-heteroatom bonds via direct C-H functionalization has emerged as an efficient methodology for the synthesis of biologically active molecules and functionalized materials.<sup>1</sup> Transition metals are commonly required to accelerate the C-H activation step,<sup>2</sup> however, the recovery and reuse of "soluble" metal catalysts can be challenging. It is therefore more beneficial that recyclable materials replace conventional homogeneous analogues as catalysts for organic transformations.<sup>3</sup> The use of heterogeneous catalysts, such as a metal organic framework-,4a-c carbon-,4d-k alumina-,<sup>41</sup> or polymer-supported catalysts,<sup>4m-n</sup> for C-H activation has been reported. However, complex catalytic systems are scarcely available and expensive second- or third-row metals are required. Few literature examples describe simple and first-row transition metal-based catalysts for C-H functionalization.<sup>5</sup> Notably, reusable, heterogeneous copper catalysis is used in these rare cases.<sup>5d-g</sup> As part of our continued interest in copperpromoted C-H activation/functionalization,<sup>6</sup> herein, we report a method for the copper ferrite nanoparticle-catalyzed, directed O-H/C-H coupling of (2-hydroxyphenyl)benzoazoles and N,Ndialkyl formamides.

In this protocol, the benzothiazole motif acts as a directing substituent, thus facilitating the coupling transformation to give a hybrid benzothiazole-carbamate moiety. Based on previous C-H functionalization reactions reported by our group,<sup>6,7</sup> copper ferrite nanoparticles were used as the catalyst and *tert*-butyl hydroperoxide (*t*BuOOH) was chosen as the oxidant.

Optimization with respect to the catalyst and oxidant is illustrated in Table 1. tBuOOH in decane (Entry 1) was an

inferior oxidant compared with *t*BuOOH in water (Entry 2). The inorganic oxidant  $K_2S_2O_8$  afforded **3** in low yield (Entry 3). Conducting the reaction at 60 °C substantially decreased the reaction yield (Entry 4), whilst decreasing the amount of oxidant still gave product **3** in good yield (Entry 5). Other heterogeneous iron-based catalysts were inferior (Entries 6-8). Finally, the reaction in air without an external oxidant was inefficient (Entry 9), and copper ferrite was found to be necessary (Entry 10).

Table 1. Optimization conditions and control experiments<sup>a</sup>

	• + • H 2	catalyst (5 mol%) oxidant (4 equiv.) 100 °C, 1 h	
Entry	Catalyst	Oxidant	Yield <b>3</b> (%)
1	Nano CuFe <sub>2</sub> O <sub>4</sub>	tBuOOH/decane (6 M)	59
2	Nano CuFe <sub>2</sub> O <sub>4</sub>	tBuOOH/water (70%)	72
3	Nano CuFe2O4	$K_2S_2O_8$	< 5
4 <sup>b</sup>	Nano CuFe2O4	tBuOOH/water (70%)	< 5
5°	Nano CuFe <sub>2</sub> O <sub>4</sub>	tBuOOH/water (70%)	76
6 <sup>c</sup>	Nano NiFe <sub>2</sub> O <sub>4</sub>	tBuOOH/water (70%)	< 5
$7^{\rm c}$	Nano Fe <sub>3</sub> O <sub>4</sub>	tBuOOH/water (70%)	N.R.
8 <sup>c</sup>	Nano Fe <sub>2</sub> O <sub>3</sub>	tBuOOH/water (70%)	N.R.
9 <sup>d</sup>	Nano CuFe <sub>2</sub> O <sub>4</sub>	-	< 5
10	-	tBuOOH/water (70%)	N.R.

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<sup>a</sup> Reagents and conditions: (2-hydroxyphenyl)benzothiazole **1** (0.5 mmol), N,N'-dimethylformamide **2** (1.5 mL), catalyst (0.025 mmol, 5 mol%), oxidant (2 mmol), 100 °C, 1 h. Yields determined by GC analysis, with diphenyl ether as the internal standard. <sup>b</sup> Temperature: 60 °C. <sup>c</sup> *I*BuOOH/water (0.5 mmol). <sup>d</sup> air as the sole oxidant. Further optimization is contained in the ESI (Table S1-2).

**Table 2.** Coupling of phenols containing the benzoazole motif and formamides<sup>a</sup>





 $^a$  Reagents and conditions: (2-hydroxyphenyl)benzoazole (0.5 mmol), dialkylformamide (19 mmol), CuFe<sub>2</sub>O<sub>4</sub> (0.025 mmol, 5 mol%), tBuOOH/water (0.5 mmol), 100 °C, 2 h. Isolated yields. See ESI for details.

2

The reaction scope with respect to the *ortho*-arylated phenols and dialkylformamides is presented in Table 2. Diethylformamide and dimethylformamide were both coupled with (2-hydroxyphenyl)benzothiazole in good yields (Entries 1-2). Steric hindrance (Entry 3) or a longer alkyl chain (Entry 4) on the formamide nitrogen did not significantly affect the reaction yield. Formamides bearing a cyclic amide moiety afforded the corresponding products in reasonable yields (Entries 5-6). Additionally, benzoxazole (Entry 7) and benzimidazole (Entry 8) were competent substrates for the reaction. In contrast to copperor iron-catalyzed, non-directed dehydrogenative coupling, the reaction of benzimidazole did not favor C-N bond formation (Entry 8).<sup>8</sup>

The research was subsequently extended to the coupling of other phenols with dialkylformamides in the presence of the copper ferrite catalyst. It was found that phenols containing carbonyl substituents at the *ortho* position were also reactive towards this transformation, affording the corresponding carbamates in reasonable yields (Entries 1-4, Table S3). However, carbonyl substituents at the *meta*- or *para*- position did not promote the coupling reaction (Entries 5-6, Table S3). Interestingly, 2-(4,5-dihydro-1*H*-imidazol-2-yl)phenol (Entries 7-8, Table S3) was inactive, with no trace of the carbamates detected. Similarly, phenol, 2-phenyl phenol, and 2-methyl phenol were also inert in this reaction (Entries 9-11, Table S3).



Figure 1. Leaching test of copper ferrite nanoparticles.



Figure 2. Reusability of the copper ferrite catalyst.

Leached homogeneous species have been reported to effect C-H functionalization reactions;<sup>9</sup> therefore control experiments were necessary to confirm the heterogeneity of the copper ferrite nanoparticles. Obviously, if additional product **3** was generated after the catalyst was separated from the reaction mixture, the contribution of homogeneous catalysis to the reaction of **1** with **2** would be significant. It was observed that upon catalyst removal after 30 min the reaction did not substantially yield additional product **3**, indicating that leaching of the active species was negligible (Fig. 1).

Additionally, recovery and reuse of the copper ferrite catalyst was demonstrated for the reaction of **1** with **2**. After the first run, the catalyst was gathered by magnetic decantation, washed carefully with DMF and MeOH, dried under vacuum, and reused in subsequent reactions. It was observed that the regenerated catalyst afforded the desired product without a significant decrease in yield; a 72% yield of compound **3** was achieved in the 9<sup>th</sup> run (Fig. 2). Moreover, the structure of the nanoparticle CuFe<sub>2</sub>O<sub>4</sub> was maintained during the reaction, as disclosed by XRD analysis (Fig. 3).



Figure 3. XRD analysis of the new (a) and recovered (b) catalyst.



Figure 4. Affect of radical scavengers.



To explore the pathway for the reaction of **1** with **2**, (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) and ascorbic acid were added to the reaction mixture after 10 min. It was found that the reaction was affected by the radical scavengers, with 26% and 38% yields of **3** obtained under these conditions (Fig. 4). These observations demonstrated that the interaction of TEMPO or ascorbic acid with the radical species generated in the catalytic cycle could stop the transformation. Furthermore, the reaction of phenol, 2-phenyl phenol, and 2-methyl phenol, respectively, with **2** did not occur (Entries 9-11, Table S3), confirming that the nitrogen functionality in **1** is actually promoting the coupling reaction. As mentioned earlier, 2-(4,5-dihydro-1*H*-imidazol-2-yl)phenol (Entries 7-8, Table S3) was unable to react with dialkylformamides, indicating the necessity of the benzene ring of the (2-hydroxyphenyl)benzoazoles to the reaction.

The reaction of 1 with 2 utilizing the nanoparticle CuFe<sub>2</sub>O<sub>4</sub> catalyst proceeded in 76% yield, while both nanoparticle Fe<sub>2</sub>O<sub>3</sub> and nanoparticle Fe<sub>3</sub>O<sub>4</sub> were inactive, suggesting that the copper sites on the CuFe2O4 superparamagnetic nanoparticles were responsible for the catalytic activity. A possible mechanism is proposed Figure 5. Chelation in of (2 hydroxyphenyl)benzothiazole to the copper sites forms a cyclometalated species.<sup>10</sup> Single-electron oxidative addition of copper(II) by the formamide radical generates a copper(III) species, which then undergoes reductive elimination to afford the product and the copper(I) species. Catalyst regeneration proceeds via oxidation of copper(I) by either peroxide or the oxygen in air.

In conclusion, we have developed a method for the copper ferrite-catalyzed, directed coupling of phenols and dialkylformamides. Benzothiazole, benzoxazole, benzimidazole and formamides bearing acyclic and cyclic substituents on nitrogen are compatible with the reaction conditions. Copper ferrite could be recovered by magnetic decantation, and reused without significant leaching. To the best of our knowledge, this transformation has not been previously performed under heterogeneous catalysis conditions.

#### Acknowledgments

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### **Copper Ferrite Superparamagnetic** Nanoparticles as a Heterogeneous Catalyst for **Directed Phenol/Formamide Coupling**

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#### **Highlights**

CuFe<sub>2</sub>O<sub>4</sub> nano particles were used as a catalyst •

for directed phenol/formamide coupling.

- High yields were obtained.
- The magnetic catalyst could be recovered and

#### **Graphical Abstract**

**Copper Ferrite Superparamagnetic** Nanoparticles as a Heterogeneous Catalyst for Directed Phenol/Formamide Coupling Chung K. Nguyen, Ngon N. Nguyen, Kien N. Tran, Viet D. Nguyen, Tung T. Nguyen, Dung T. Le, and Nam T. S. Phan CuFe<sub>2</sub>O<sub>4</sub> (5 mol%) tBuOOH (1 equiv.) 120 °C, 2 h MANU