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Communication

Room temperature multicomponent synthesis of diverse propargylamines using magnetic $CuFe_2O_4$ nanoparticle as an efficient and reusable catalyst

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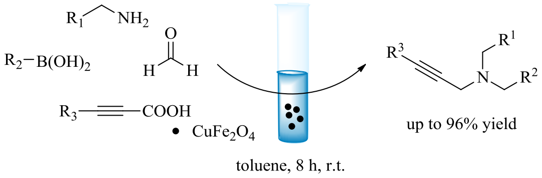
Graphical abstract



We report the magnetic recoverable catalyst ($CuFe_2O_4$) catalyzed multicomponent reaction of aliphatic amines, formaldehyde, arylboronic acids and alkynyl carboxylic acids for the synthesis of diverse propargylamines at room temperature.

ABSTRACT

Copper ferrite ($CuFe_2O_4$) nanoparticles catalyzed room temperature multicomponent reaction of aliphatic amines, formaldehyde, arylboronic acids and alkynyl carboxylic acids was reported for the synthesis of diverse propargylamines with good to excellent yields. The catalyst can be magnetically recovered and reused at least five times without significant loss of activity.

Keywords: Multicomponent reaction, Magnetic catalyst, Recycle, Copper ferrite, Propargylamine

Catalysts are widely used to provide energy efficient, selective, atom-economical solutions to many industrially important problems in organic chemistry synthesis [1]. Recently, magnetic nanoparticles, which can be easily separated and recycled by external magnet, have been efficiently employed as heterogeneous catalysts and supports of catalysts in many chemical reactions [2]. Compared to filtration or centrifugation, magnetic separation handles easily and can increase the reusability. And it is generally recognized that the use of these nanosized magnetic particles provides both economical and ecological benefits [3]. Among the magnetic nanoparticle catalysts, the direct use of magnetic metal oxide nanoparticles as catalysts has attracted more and more attention. In 2010, Sreedhar reported Fe_3O_4 nanoparticles catalyzed three-component coupling of aldehyde, amine, and alkyne through C-H activation for the

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synthesis of propargylamines [4]. In 2016, Wang reported a green and efficient protocol for the $CuFe_2O_4$ nonparticle-catalyzed direct C(sp^3)-H bond functionalization of 2-alkyl azaarenes [5]. Recently, Moghaddam reported the synthesis of unsymmetrical sulfides *via* $CoFe_2O_4$ catalyzed cross-coupling reaction of nitroarenes with alkyl halides in the presence of thioureac [6]. Besides, $MnFe_2O_4$, $NiFe_2O_4$ are also used as catalysts in various reactions [7,8].

Multicomponent coupling reactions (MCRs), generally with high atom economy, selectivity and flexibility, have been a powerful synthetic tool to access complex structures from simple precursors *via* a one-pot procedure, and in general [9]. Among those MRCs, the A^3-coupling of aldehydes, amines and alkynes has received considerable attention in recent years [10]. More importantly, the resultant propergylamines are versatile synthetic intermediates for various nitrogen compounds [11] and other biologically active compounds such as *β*-lactams, conformationally restricted peptides, isosteres, natural and therapeutic drug molecules [12]. Meanwhile, impregnated copper on magnetite has been reported to be a heterogeneous and reusable copper-based catalyst for the A^3-coupling [13].

Recently, we reported a metal-free decarboxylative coupling reaction for the synthesis of propargylamines from the four-component reaction of amine, aldehyde, arylboronic acid and alkynyl carboxylic acid [14]. Though the yields were acceptable, long reaction time, high temperature and nitrogen atmosphere are need. Considering the use of highly efficient, economic and recoverable catalysts, which can promote the reaction in more mild conditions, conforms to the concept of green chemistry, we envisioned that copper ferrite nanoparticles would activate the transformation and a more efficient and fast one-pot approach to the tertiary proparglyamines would be obtained.

As part of our ongoing interest in the synthesis of propargylamines, we reported our investigation on the application of copper ferrite ($CuFe_2O_4$) nanoparticles for the practical and atom-economic synthesis of propargylamines through four-component coupling of amines, formaldehyde, arylboronic acids and alkynyl carboxylic acid (Scheme 1). At the end of reaction, the $CuFe_2O_4$ nanoparticles can be easily recycled by an external magnet and reused without obvious loss of catalytic activity (the preparation of nano $CuFe_2O_4$ has been provided in the Supporting information).

In a preliminary reaction, benzylamine (1 mmol) was treated with formaldehyde (2.5 mmol), phenylboronic acid (1.5 mmol) and phenylpropiolic acid (1.3 mmol) in the presence of $CuFe_2O_4$ nanoparticles (10 mol %) in toluene (2.5 mL) for 8 h at room temperature. The reaction conditions were optimized by varying the ratio of reactants, reaction time, and the amount of $CuFe_2O_4$. Investigation on the ratio of reactants, the best yield was obtained when benzylamine, formaldehyde, phenylboronic acid and phenylpropiolic acid proceeded under the ratio of 1: 2.5: 1.5: 1.3 (Table 1, entry 3), while decreasing or increasing the ratio of phenylboronic acid or phenylpropiolic acid did not improve the reaction yields (Table 1, entries 1-5). While the reaction time was reduced from 8 h to 4 h, the product yield decreased from 96% to 65%. (Table 1, entries 3, 6 and 7). In the absence of the catalyst, only 6% yield was obtained. Decreasing the amount of $CuFe_2O_4$ from 10 mol% to 5 mol%, the product yield was decreased, while increasing to 15 mol%, the yield was not improved significantly (Table 1, entries 3, 8, 9 and 10). Finally, the reaction conditions were optimized to be $CuFe_2O_4$ (10 mol%) as catalyst, benzylamine reacted with formaldehyde, phenylboronic acid, phenylpropiolic acid with the ratio of 1: 2.5: 1.5: 1.3, and reaction for 8 h at room temperature (Table 1, entry 3).

To assess the generality of this approach, various amines, arylboronic acids and propiolic acids were applied under the optimized reaction conditions as summarized in Table 2 (characterization of selected products and typical experiments have been provided in the Supporting information). Firstly, various primary amines were applied in this reaction (Table 2， entries 2-5). Benzylamine derivatives, with electronic-withdrawing or donating groups such as fluoro, methyl, and trifluoromethyl on the benzene ring, afforded the desired products in good yields. Naphthalen-1-ylmethanamine produced corresponding product in 72% (Table 2, entry 6). Aromatic heterocycles such as pyridinyl and other aliphatic amines were also applicable with lower yields (Table 2, entries 7-9). Afterwards,

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four-component coupling reactions of various arylboronic acids with benzylamine, formaldehyde and phenylpropiolic acid were examined (Table 2, entries 10-15).

Generally, electronic-donating substituents (-OMe) bound to the benzene ring furnished higher yields and short reaction time, while arylboronic acids with electronic-withdrawing groups (-Cl and -F) decreased the reactivity and a longer reaction time was required to obtain moderate yields (Table 2, entries 10 and 12). Furthermore, (*E*)-styrylboronic acid could be employed to deliver 1,6-enyne product (Table 2, entry 13) with 72% yield. Unfortunately, aromatic heterocycle and aliphatic boronic acids shut down the reaction (Table 2, entries 14-15). Subsequently, the scope of propiolic acids was investigated (Table 2, entries 16-19). Both arylpropiolic acids and aliphatic propiolic acid produced desired products with satisfactory yields. Finally, the multicomponent reaction was applied in construction of diverse propargylamines (Table 2, entries 20-23).

On the basis of previously reports [16], we propose a plausible mechanism as shown in Scheme 2. The reaction of primary amine **1**, formaldehyde **2**, and organoboronic acid **3** afforded a secondary amine **6** *via* the PBM reaction [17], the intermediate 6 could undergo a second PBM reaction with formaldehyde **2** and organoboronic acid **3** to produce the byproduct **7** which was detected by GC-MS [18]. The reaction of the secondary amine **6** and formaldehyde **2** generated hemiaminal **B**. The decarboxylation process is initiated by cation exchange between propiolic acid **4** and the copper salt affording copper species **D**. Cu(Ⅱ)-catalyzed decarboxylation of **D** to alkynylcopper **E** followed by coupling reaction with iminium salt **C** affording propargylamine copper complex **F** [13b]. The final desired propargylamine was generated from intermediate **F** along with the regeneration of the Cu(Ⅱ) catalyst.

The multicomponent reaction of benzylamine, formaldehyde, phenylboronic acid and phenylpropiolic acid was performed to test the reusability of the catalyst, After each reaction, $CuFe_2O_4$ was magnetically recovered, washed with ethanol, air-dried and reused directly for the next time. As shown in Fig. 1, after five times reuse, no obvious loss of activity was observed.

In conclusion, we have developed a simple and efficient method for the synthesis of propargylamines *via* magnetically separable $CuFe_2O_4$ catalyzed multicomponent reaction of amine, formaldehyde, arylboronic acid and alkynyl carboxylic acid. The reaction proceeds smoothly with good to excellent yields at room temperature under air atmosphere. And the catalyst can be magnetically recovered and reused for four times without obvious loss of activity. All these features make the present method a useful complementary pathway for the synthesis of propargylamines.

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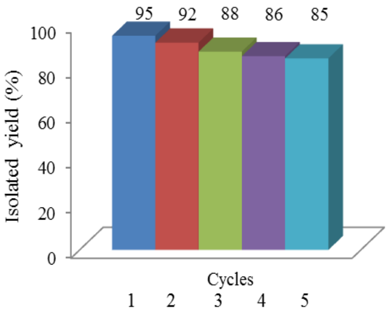
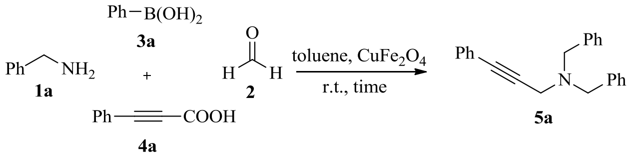
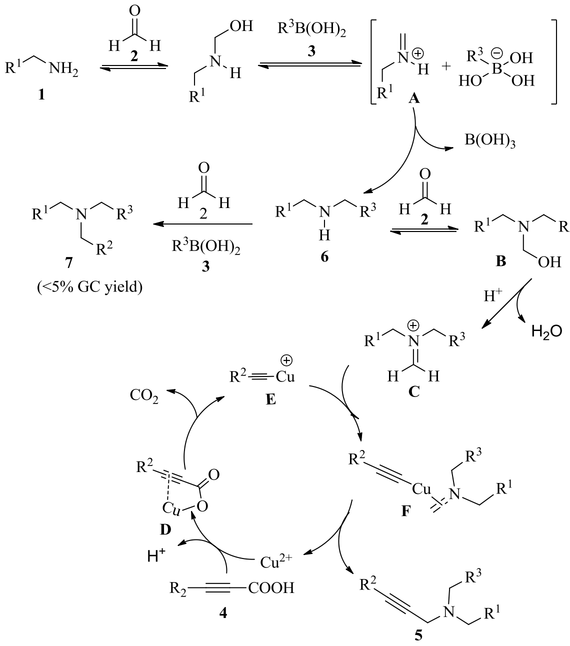


Fig. 1. Recycle and reuse of the catalyst in the synthesis of *N*,*N*-dibenzyl-3-phenylprop-2-yn-1-amine.



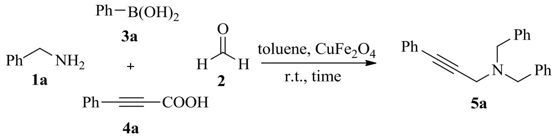
Scheme 1. $CuFe_2O_4$ catalyzed synthesis of propargylamines.



Scheme 2. Tentative mechanism for the magnetic $CuFe_2O_4$ catalyzed reaction.

Table 1

Optimization of the reaction conditions.[a]



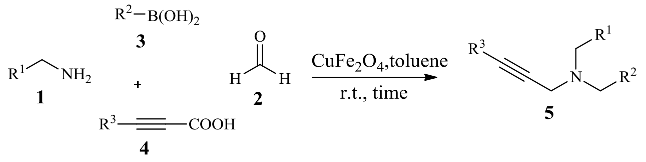
Entry	**1a/2/3a/4a** (Ratio)	Time (h)	$CuFe_2O_4$ (mol%)	Yield (%)[b]
1	1/2.5/1.4/1.3	8	10	88
2	1/2.5/1.6/1.3	8	10	90
3	1/2.5/1.5/1.3	8	10	96
4	1/2.5/1.5/1.5	8	10	95
5	1/2.5/1.5/1.1	8	10	78
6	1/2.5/1.5/1.3	6	10	85
7	1/2.5/1.5/1.3	4	10	65
8	1/2.5/1.5/1.3	8	0	6
9	1/2.5/1.5/1.3	8	5	85
10	1/2.5/1.5/1.3	8	15	97

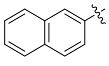
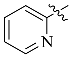
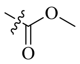
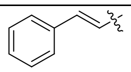
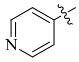
[a] Reaction conditions: benzylamine (1 mmol), formaldehyde (40% aqueous solution), phenylpropiolic acid, phenylboronic acid, toluene (2.5 mL), room temperature, and air atmosphere.

[b] Yields were determined by GC analysis using dodecane as internal standard.

Table 2

Scope of the multicomponent reaction of primary amines, boronic acids, formaldehyde and propiolic acids. [a]



Entry	R^1	R^2	R^3	Product	Yield (%) [b]
1	Ph	Ph	Ph	**5a**	95
2	*p*-F-Ph	Ph	Ph	**5b**	90
3	*p*-CF_3-Ph	Ph	Ph	**5c**	72
4	*p*-CH_3-Ph	Ph	Ph	**5d**	92
5	*o*-Cl-Ph	Ph	Ph	**5e**	75
6		Ph	Ph	**5f**	72
7		Ph	Ph	**5g**	45
8	$CH_3CH_2CH_2$	Ph	Ph	**5h**	48
9		Ph	Ph	**5i**	32
10[c]	Ph	*p*-Cl-Ph	Ph	**5j**	70
11	Ph	*p*-MeO-Ph	Ph	**5k**	96
12[c]	Ph	2,4-diF-Ph	Ph	**5l**	52
13[d]	Ph		Ph	**5m**	72
14[c]	Ph		Ph	**5n**	0
15[c]	Ph	$CH_3CH_2CH_2CH_2$	Ph	**5o**	0
16[c]	Ph	Ph	*p*-CH_3- Ph	**5p**	85
17[c]	Ph	Ph	*p*-Cl-Ph	**5q**	72
18	Ph	Ph	*p*-NO_2-Ph	**5r**	65
19	Ph_4	Ph	CH_3CH_2	**5s**	71
20	Ph	*p*-CH_3O-Ph	*p*-Cl-Ph	**5t**	87
21	*p*-CF_3- Ph	*p*-F-Ph	Ph	**5u**	87
22	*p*-CH_3-Ph	*p*-CH_3O-Ph	Ph	**5v**	90
23	*p*-CH_3O-Ph	*p*-CH_3O-Ph	*p*-Cl-Ph	**5w**	78

[a] Reaction conditions: amine (1 mmol), formaldehyde (40% aqueous solution, 2.5 mmol), propiolic acid (1.3 mmol), arylboronic acid (1.5 mmol), toluene (2.5 mL), 8 h at room temperature.

[b] Isolated yields based on amines.

[c] The reaction time is 20 h.

[d] Reaction was performed at 40 ºC for 12 h in a sealed tube