Synthesis of Propargylamines by Three-Component Coupling of Aldehydes, Amines and Alkynes Catalyzed by Magnetically Separable Copper Ferrite Nanoparticles

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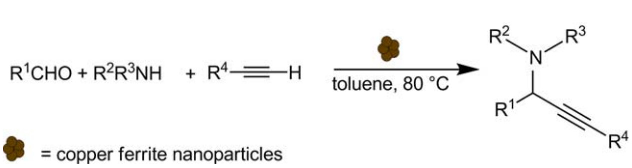
Abstract: An efficient three-component coupling of aldehydes, amines and alkynes has been developed to prepare propargylamines in nearly quantitative yields using magnetically separable copper ferrite nanoparticles as catalyst. Structurally divergent aldehydes and amines were converted into the corresponding propargylamines. The reaction does not require any co-catalyst.

Key words: copper ferrite nanoparticles, propargylamines, three-component coupling, reusability

Despite the advantages of homogeneous metal catalysts, difficulties in recovering the catalyst from the reaction mixture severely inhibits their wide use in industry. Heterogeneous catalysis supplies the opportunity for easy separation and recycling of the catalyst, easy purification of product and the possibility of continuous or multiple processing of compounds. Magnetic nanoparticles that can be magnetized in the presence of an external magnet have been studied extensively for various biological applications such as magnetic resonance imaging, drug delivery, biomolecular sensors, bioseparation and magnetothermal therapy.[1] Recent reports show that magnetic nanoparticles are efficient supports and can facilitate catalyst separation from the reaction medium after magnetization with a permanent magnetic field.[2]

One-pot multicomponent coupling reactions (MCR) where several organic moieties are coupled in one step is an attractive synthetic strategy.[3] Three-component coupling of aldehydes, amines and alkynes (A^3 coupling) is one of the best examples of MCR, and has received much attention in recent times. The resultant propargylamines obtained by A^3 coupling reactions are versatile synthetic intermediates for biologically active compounds such as β-lactams, conformationally restricted peptides, isosteres, natural products and therapeutic drug molecules.[4] Traditionally, propargylamines are prepared by amination of propargylic halides, propargylic phosphates or propargylic triflates.[5] However, these reagents are used in stoichiometric amounts, are highly moisture sensitive and require strictly controlled reaction conditions. Recently, mild metal-catalyzed reactions based upon the nucleophilic addition of metal acetylides generated in situ, to imines and enamines have been reported for the synthesis of propargylamines.[6] Carreira and Fischer demonstrated the preparation of propargylamines by the reaction of aldimines with trimethylsilyl acetylene by using commercially available and air-stable $[IrCl(Cod)]_2$.[7] Wei and Li reported the A^3 coupling reaction through C–H bond activation in water using gold, silver and silver in ionic liquids without using any noble metal co-catalyst.[8] Though the yields were good, the scope is generally limited for cyclic amines in the silver-catalyzed reaction, and inert conditions are invariably used for the gold- and silver-catalyzed reactions in order to obtain good yields. More recently, Tu and co-workers developed a microwave (MW) promoted CuI catalyzed A^3 coupling reaction.[9] A chiral version of the A^3 coupling reaction for the formation of chiral propargylamines is also reported using copper and gold complexes as chiral catalysts under homogeneous conditions.[10] Recently, we reported the A^3 coupling reaction using heterogeneous catalysts such as copper supported on hydroxyapatite,[11] layered double hydroxide supported gold,[12] and zinc dust[13] for the preparation of propargylamines.

As part of our ongoing research aimed at the development of reusable catalysts for various organic transformations,[14] we herein explore the activity of copper ferrite nanoparticles for the A^3 coupling reaction to generate propargylamines without using any co-catalyst or additive (Scheme 1).



Scheme 1

Initially, in order to identify and develop the best magnetically separable catalyst for the synthesis of propargylamines by A^3 coupling reaction, Fe_3O_4 and different substituted ferrites, MFe_2O_4 ($M = Cu^{2+}, Co^{2+}, Ni^{2+}$) were synthesized by co-precipitation methods as described in the literature[15,16] and screened in the presence of benzaldehyde, piperidine and phenylacetylene. The results are summarized in Table 1. It was found that Fe_3O_4, $CoFe_2O_4$ and $NiFe_2O_4$ gave lower yields, while $CuFe_2O_4$ nanoparticles afforded excellent yields in short periods of time (Table 1, entries 1, 7, 8 and 9). When the $CuFe_2O_4$ nanoparticle-catalyzed A^3 coupling reaction was carried out in

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solvents other than toluene, such as anhydrous THF, dioxane, acetonitrile or 1,2-dichloroethane (DCE), a significant decrease in yield was noticed. When water was used as a solvent, only a trace amount of product was observed even after prolonged reaction time. The optimum ratio of aldehyde, amine and alkyne was found to be 1:1.2:1.3, respectively. The catalytic activity of the $CuFe_2O_4$ nanoparticles was evident when no product was obtained in the absence of catalyst. The feasibility of repeated use of $CuFe_2O_4$ was also examined. In Table 2, results from the investigation of $CuFe_2O_4$ for three consecutive cycles of the same reaction are presented. After each cycle, nanoparticles were magnetically separated, washed, air-dried and used directly for the next cycle of reaction without further purification. No significant loss of catalytic activity was observed for $CuFe_2O_4$ in the A^3 coupling reactions.

Table 1 Three-Component Coupling of Benzaldehyde, Piperidine and Phenylacetylene with Various Catalysts and Solvents[a]

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	$CuFe_2O_4$	toluene	4	86
2	$CuFe_2O_4$	MeCN	6	25
3	$CuFe_2O_4$	THF	10	trace[c]
4	$CuFe_2O_4$	dioxane	10	trace
5	$CuFe_2O_4$	DCE	6	31
6	$CuFe_2O_4$	H_2O	10	trace
7	Fe_3O_4	toluene	4	15
8	$NiFe_2O_4$	toluene	4	trace
9	$CoFe_2O_4$	toluene	4	trace

[a] Reaction conditions: Benzaldehyde (1 mmol), piperidine (1.2 mmol), phenylacetylene (1.3 mmol), solvent (4 mL), $CuFe_2O_4$ nanoparticles (15 mg, 6.5 mol%), 80 °C, N_2 atmosphere.
[b] Isolated yield.
[c] Reflux temperature.

Table 2 Recycling of the Catalytic System for the Three-Component Coupling of Benzaldehyde, Piperidine and Phenylacetylene[a]

Run	Catalyst recovery (%)	Isolated yield (%)
1	–	86
2	93	81
3	91	78

[a] Reaction conditions: Benzaldehyde (1 mmol), piperidine (1.2 mmol), phenylacetylene (1.3 mmol), toluene (4 mL), $CuFe_2O_4$ nanoparticles (15 mg, 6.5 mol% of copper), 80 °C, 4 h, N_2 atmosphere.

Atomic absorption spectroscopy (AAS) was employed to determine the copper content of $CuFe_2O_4$ nanoparticles, and it was found to be 27.32%. The leaching of the metal after the first cycle was determined by AAS and was found to be negligible (0.258%). The general applicability of the $CuFe_2O_4$ nanoparticle-promoted A^3 coupling reaction was illustrated when a variety of structurally divergent aldehydes and amines possessing a wide range of functional groups were used.[17] As summarized in Table 3, both aromatic and aliphatic aldehydes were able to undergo addition to afford the corresponding propargylic amines effectively. The results in Table 3 indicate that aromatic aldehydes bearing different functional groups such as chloro, bromo, or methoxy were able to affect the A^3 coupling. Trace amount of product was obtained when 4-nitrobenzaldehyde was used as a substrate, increasing the reaction time did not increase the yield.

The aliphatic aldehyde (Table 3, entry 8) displayed high reactivity and the corresponding propargylamine was obtained in high yields. Heteroaromatic aldehydes such as furfuraldehyde and 3-pyridinecarboxaldehyde reacted with piperidine and phenylacetylene to afford the corresponding propargylamines in good yields (Table 3, entries 9 and 10).

Table 3 Three-Component Coupling between Piperidine, Phenylacetylene and Various Aldehydes Catalyzed by $CuFe_2O_4$ Nanoparticles[a]

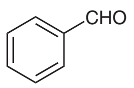
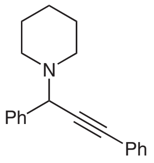
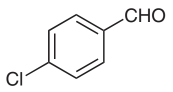
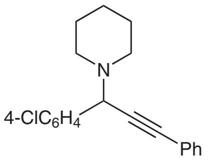
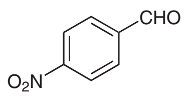
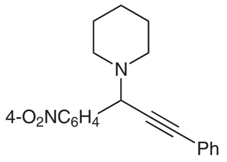
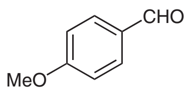
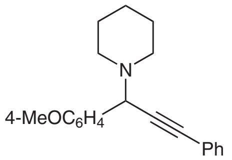
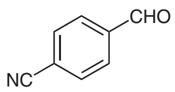
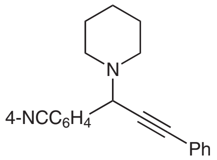
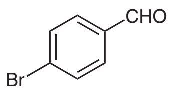
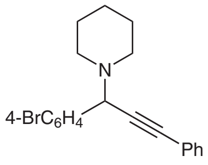
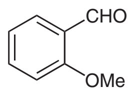
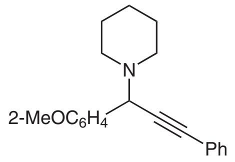
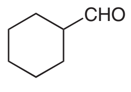
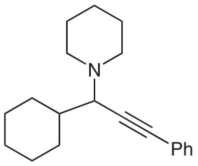
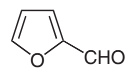
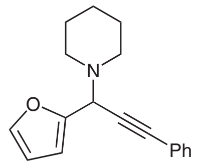
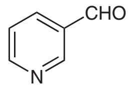
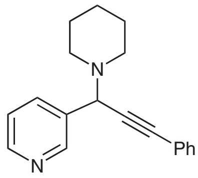
Entry	Aldehyde	Product	Time (h)	Yield (%)[b]
1			4	86
2			4	88
3			12	trace
4			15	85
5			7	90
6			5	84

Table 3 Three-Component Coupling between Piperidine, Phenylacetylene and Various Aldehydes Catalyzed by $CuFe_2O_4$ Nanoparticles[a] (continued)

Entry	Aldehyde	Product	Time (h)	Yield (%)[b]
7			15	89
8			5	91
9			5	81
10			5	83

[a] Reaction conditions as exemplified in the typical experimental procedure.[17]

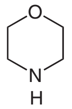
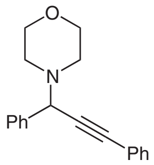
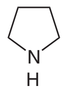
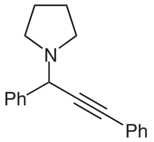
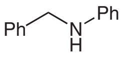
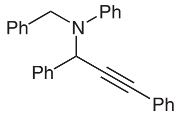
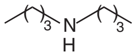
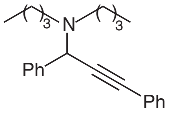
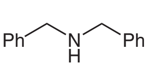
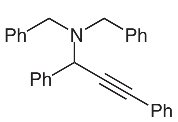
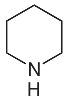
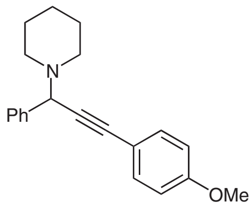
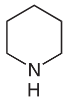
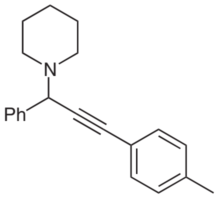
[b] Isolated yield.

Different amine substrates, such as morpholine, pyrrolidine and dibutylamine gave very good yields of the coupling products in the A^3 coupling reaction of benzaldehyde and phenylacetelene (Table 4, entries 1, 2 and 4). On the other hand, aromatic amines, such as dibenzylamine or phenylbenzylamine gave moderate yields of the product (Table 4, entries 3 and 5). There was not much difference in the yield when the aryl group of the phenylacetylene was substituted with a 4-methoxy or 4-methyl group (Table 4, entries 6 and 7).

Figure 1 shows two TEM images of the $CuFe_2O_4$ catalyst before and after use. It can be observed that the synthesized particles are spherical, about 10–12 nm in size, and that the morphology and size of the particles do not change considerably even after recycling.

It is assumed that the A^3 coupling reaction proceeds by terminal alkyne C–H bond activation by the $CuFe_2O_4$ nanoparticles.[8] The copper acetylide intermediate thus generated will react with the iminium ion prepared in situ from the aldehyde and the amine and form the corresponding propargylamine, water and $CuFe_2O_4$ nanoparticles. Thus, the regenerated $CuFe_2O_4$ nanoparticles participate further in the reaction and complete the catalytic cycle.

Table 4 Three-Component Coupling between Benzaldehyde and Various Amines and Alkynes Catalyzed by $CuFe_2O_4$ Nanoparticles[a]

Entry	Amine	Product	Time (h)	Yield (%)[b]
1			4	85
2			4	81
3			7	71
4			12	87
5			15	65
6			8	75
7			8	71

[a] Reaction conditions as exemplified in the typical experimental procedure.[17,]

[b] Isolated yield.

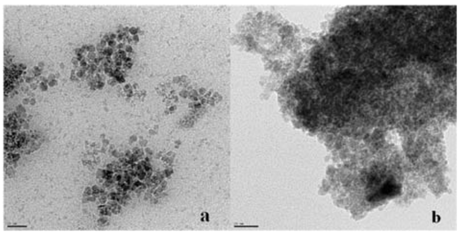


Figure 1 TEM figures of copper-ferrite nanoparticles: (a) before use, (b) after use

In summary, an efficient $CuFe_2O_4$ nanoparticle-catalyzed three-component coupling of aldehydes, amines and alkynes has been achieved in toluene. Both aliphatic as well as aromatic aldehydes and amines can be used. The catalyst is magnetically separated and reused for several cycles with only a slight decrease in activity.

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(16) **Typical procedure for the preparation of $CuFe_2O_4$ nanoparticles:** $CuFe_2O_4$ nanoparticles were prepared by a soft chemical method – co-precipitation of Fe^{2+} and Cu^{2+} cations in strong alkaline media at room temperature.[15a] Dilute water solutions of $FeCl_2·4H_2O$ and $CuCl_2·2H_2O$ mixed in the ratio 2:1 with intensive stirring were used for that purpose. In a water solution, the chlorides of these elements exist in a complex form. When a concentrated solution of NaOH with pH 13 is added, the complexes turn into hydroxides and a black precipitate of $CuFe_2O_4$ is produced. After decanting, the precipitate is rinsed with distilled water until pH 7 and then dried.

(17) **Typical procedure for A^3 coupling reaction:** A mixture of benzaldehyde (1 mmol), piperidine (1.2 mmol), phenylacetylene (1.3 mmol) and $CuFe_2O_4$ nanoparticles (15 mg, 6.5 mol% of copper) in toluene (4 mL) was stirred in a round-bottomed flask at 80 °C under N_2 atmosphere. After completion of the reaction, which was monitored by TLC, the reaction mixture was magnetically concentrated with the aid of a magnet to separate the catalyst and the catalyst was washed several times with Et_2O. The reaction mixture was concentrated under reduced pressure to afford the crude product which, after chromatography on silica gel, gave the corresponding propargylamine, *N*-(1,3-diphenyl-2-propynyl)piperidine. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.64–7.56$ (m, 2 H), 7.50–7.42 (m, 2 H), 7.36–7.18 (m, 6 H), 4.76 (s, 1 H), 2.55–2.52 (m, 4 H), 1.63–1.54 (m, 4 H), 1.51–1.42 (m, 2 H). ESI MS: $m/z = 276\ (M + H)^+$.