Fe_3O_4 nanoparticles: a robust and magnetically recoverable catalyst for three-component coupling of aldehyde, alkyne and amine

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A robust, safe and magnetically recoverable Fe_3O_4 nanoparticle catalyzed three-component coupling of aldehyde, alkyne, and amine (A^3-coupling) was developed. A diverse range of propargylamines were obtained in moderate to high yield under mild conditions in air. The separation and reuse of the magnetic Fe_3O_4 nanoparticles were very simple, effective and economical.

Environmentally benign, economical, practical, and efficient processes for catalyst separation and reuse have been increasingly important goals in the chemical community from economic, safety, and environmental points of view.[1] The strategy of magnetic separation, taking advantage of magnetic nanoparticles, is typically more effective than filtration or centrifugation as it prevents loss of the catalyst.[2] Magnetic separation of the magnetic nanoparticles is simple, economical and promising for industrial applications.[3] In recent years, Fe_3O_4 nanoparticles (magnetite nanoparticle) have attracted worldwide attention.[3] Various strategies have successfully demonstrated the applications of Fe_3O_4 nanoparticle-immobilized or -supported catalysts.[4] However, the direct use of Fe_3O_4 nanoparticles without modification as magnetically recoverable catalysts for organic reactions is very rare.[5]

Propargylic amines, products of the three-component aldehyde–alkyne–amine coupling (A^3-coupling), are useful building blocks and important skeletons of biologically active compounds.[6] During the past decade, significant efforts have been made in order to develop one-pot multi-component reactions to make new carbon–carbon bonds.[7] In the past few years, we[8] and others[9] have reported highly efficient couplings catalyzed by various metals such as copper, silver, gold, iridium, and indium to afford various propargylamines. Recently, we[10] and others[11] also reported that such a coupling can also be catalyzed by iron salts. In these studies, we also observed that iron powder could catalyze the reaction. To rationalize this result, we speculated that the iron-powder reaction was due to the catalytic activities of iron oxides on the surface of the powder. Consequently, we were intrigued by the possibility of using Fe_3O_4 nanoparticles as catalysts for the A^3-coupling reaction, featuring both a much greater surface area than iron powder and magnetic recoverability. Herein, we wish to report the robust and magnetically recoverable Fe_3O_4 and Fe_2O_3 nanoparticles catalyzed three-component coupling of aldehyde, alkyne and amine (Fig. 1). It was found that good yields were obtained and the magnetic recovery of Fe_3O_4 nanoparticles was simple and efficient. The catalyst was directly reused 12 times without the need for activation. Fe_2O_3 nanoparticles were also effective as catalysts.

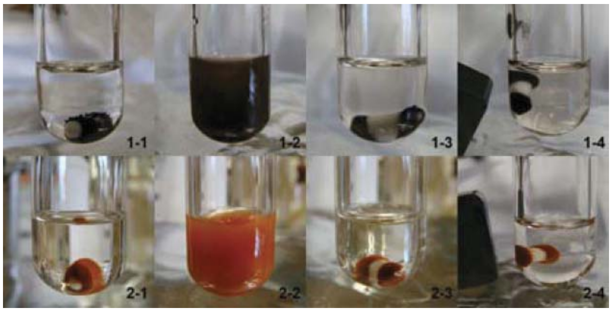

Fig. 1 Photo of 1-1: Fe_3O_4 nanoparticles in THF; 1-2: Fe_3O_4 nanoparticle dispersion in THF; 1-3: Fe_3O_4 nanoparticles adsorbed on the magnetic stirring bar; 1-4: a magnet attracted the magnetic stirring bar and Fe_3O_4 nanoparticles; 2-1: Fe_2O_3 nanoparticles in THF; 2-2: Fe_2O_3 nanoparticle dispersion in THF; 2-3: Fe_2O_3 nanoparticles adsorbed on the magnetic stirring bar; 2-4: a magnet attracted the magnetic stirring bar and Fe_2O_3 nanoparticles.

We used cyclohexanecarbaldehyde, piperidine, and phenylacetylene as standard substrates to search for a suitable solvent for the Fe_3O_4 nanoparticle (<50 nm) catalyzed A^3-coupling (Table 1). Among the solvents tested, tetrahydrofuran was the most effective reaction medium for this three-component coupling reaction (Table 1, entry 1). The use of tetrahydrofuran effected not only the coupling reaction of aldehyde, alkyne, and amine in good yield, but also performed well in the process of magnetic separation of nanoparticle catalysts, by reducing the viscosity of the reaction mixture and facilitating the congregation of magnetic catalyst, when the reaction was complete. Slightly lower yields were obtained when using acetonitrile or ethyl acetate as the solvent (Table 1, entries 2 and 3). Ethanol, dichloromethane, water, acetone and dimethyl sulfoxide (DMSO) afforded the products in only low or moderate yields (Table 1, entries 4–8). No desired product was detected by NMR when the reaction was carried out in N,N-dimethylformamide (DMF) (Table 1, entry 9). The corresponding product was also obtained in good yield under

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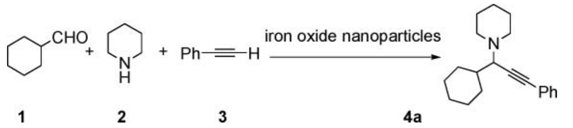
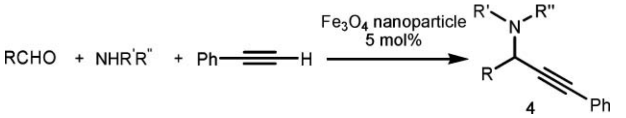
Table 1 Three-component coupling of cyclohexanecarbaldehyde, piperidine, and phenylacetylene catalyzed by a magnetic iron oxide catalyst[a]

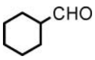
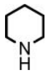
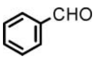
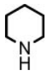
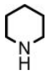
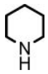
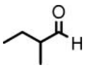
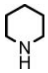
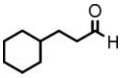
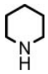
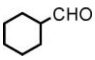
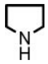
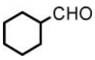
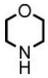
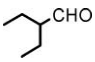
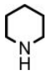
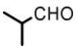
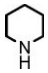
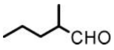
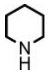
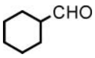
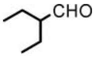
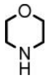
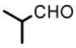
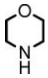


Entry	Solvent	NMR Yield(%)
1	THF	89
2	CH_3CN	86
3	Ethyl acetate	84
4	CH_3CH_2OH	69
5	CH_2Cl_2	42
6	H_2O	39
7	Acetone	29
8	DMSO	10
9	DMF	0
10	—	89
11	—	92[b]
12	THF	70[c]

[a] All reactions were carried out with cyclohexanecarbaldehyde (0.5 mmol), piperidine (0.6 mmol), phenylacetylene (0.75 mmol) and Fe_3O_4 nanoparticles (0.025 mmol) at 80 °C (oil bath) at 24 h. [b] (0.05 mmol) Fe_3O_4 nanoparticles was used as catalyst. [c] (0.025 mmol) Fe_2O_3 nanoparticles was used as catalyst.

Table 2 Three-component coupling of aliphatic aldehyde, amine, and alkyne catalyzed by iron oxide nanoparticles[a]



Entry	Aldehyde	Amine	Isolated yield (%)
1			82
2			45
3	HCHO		80
4	$CH_3(CH_2)_3CHO$		74
5			51
6			83
7			63
8			84
9			86
10			53
11			50
12			89
13			78
14			52

[a] All reactions were carried out with aldehyde (0.5 mmol), amine (0.6 mmol), alkyne (0.75 mmol) and Fe_3O_4 nanoparticles (0.025 mmol) at 80 °C (oil bath) in THF for 24 h.

neat conditions (Table 1, entry 10). However, the mixture was viscous in the absence of a solvent and made the separation of catalyst from products difficult magnetically unless an extraction solvent such as ether was added. No significant difference was observed when slightly increasing the catalyst loading (Table 1, entry 11). It is worth noting that γ-Fe_2O_3 nanoparticles (<50 nm) also catalyzed the reaction, affording the corresponding propargylamine products in a lower yield (Table 1, entry 12). The gamma-form iron oxide nanoparticles can also be separated easily by magnetic method and reused. No desired product was obtained in the absence of Fe_3O_4 nanoparticles or Fe_2O_3 nanoparticles. The optimized reaction conditions include 1.0 equiv of aldehyde, 1.2 equiv of amine, 1.5 equiv of alkyne, and 5 mol % of Fe_3O_4 nanoparticles in THF at 80 °C in air. Buchwald and Bolm recently found that the results of $FeCl_3$-catalyzed reactions may be due to trace quantities of copper.[12] To preclude such a possibility in the present case, we tested 99.99% Fe_3O_4 powder (from Aldrich) to catalyze the three-component coupling of Cu-free cyclohexanecarbaldehyde, piperidine, and phenylacetylene under the optimized reaction conditions, which gave 57% NMR yield.[13] In comparison, a 54% NMR yield was obtained when 600 ppm Cu_2O was added into this 99.99% Fe_3O_4 powder, which indicated that trace quantity of copper has no obvious effect on this reaction. Considering Fe_3O_4 nanoparticles have a much larger surface area than their powder form, we conclude that the reaction was catalyzed by Fe_3O_4 nanoparticles rather than by trace copper impurities.

To expand the scope of this A^3-coupling, various aldehydes and amines were used as substrates under the optimized reaction conditions, and the results are summarized in Table 2. In general, both aromatic and aliphatic aldehydes underwent the addition reaction smoothly to provide the desired product in moderate to good yields (Table 2, entries 1–14). However, similar to the $FeCl_3$-catalyzed A^3-coupling,[10] the reaction was found to be strongly influenced by the nature of the aldehyde. As shown in Table 2, aliphatic aldehydes were more reactive

Table 3 The reuse of Fe_3O_4 nanoparticles in A^3-coupling[a]

Cycle	NMR Yield(%)	Cycle	NMR Yield(%)
1	89	7	73
2	85	8	74
3	82	9	79
4	83	10	78
5	80	11	80
6	77	12	82

[a] All reactions were carried out with 0.5 mmol cyclohexanecarbaldehyde, 0.6 mmol piperidine, 0.75 mmol phenylacetylene and 0.025 mmol Fe_3O_4 nanoparticles (for cycle 1) or recovered Fe_3O_4 nanoparticles (for other cycles) at 80 °C (oil bath) in THF for 24 h.

than the aromatic aldehyde. The reactions involving aliphatic aldehydes such as cyclohexanecarboxaldehyde, valeraldehyde, isobutyraldehyde, 2-methylbutanal, and 3-phenylpropanal all provided higher yields than benzaldehyde (Table 2, entries 1, 2, 4, 5, 6 and 10). Formaldehyde (37 wt% in water) afforded the desired products also in good yield (Table 2, entry 3). Moderate to good yields were observed when cyclic dialkylamines such as pyrrolidine, morpholine and azepane were used (Table 2, entries 7, 8, 12, 13 and 14).

The magnetic Fe_3O_4 or Fe_2O_3 nanoparticles were adsorbed onto the magnetic stirring bar when the magnetic stirring was stopped. The nanoparticles were then washed with ethyl acetate, air-dried and used directly for the next round of reactions without further purification. It was shown that the Fe_3O_4 nanoparticle catalyst could be recovered and reused 12 times without significant loss of catalytic activity (Table 3).

In summary, we have demonstrated a robust and magnetically recoverable Fe_3O_4 nanoparticle catalyzed three-component coupling of aldehyde, alkyne, and amine (A^3-coupling). A diverse range of propargylamines were obtained in moderate to high yield under mild conditions in air. The separation and reuse of the magnetic Fe_3O_4 nanoparticles were very simple, effective and economical. In addition, the use of iron oxides as catalysts is also more environmentally friendly and safer than other transition-metal catalysts. We also showed that the efficiency of the catalytic activity is also affected by the different forms of iron oxides. The direct use and recycling of magnetic Fe_3O_4 and Fe_2O_3 nanoparticles to catalyze other reactions by the same strategy are under investigation in our laboratory.

Experimental section

Fe_3O_4 (<50 nm particle size (TEM), ≥98%) and Fe_2O_3 (<50 nm particle size) were purchased from Sigma-Aldrich. To a reaction tube charged with a magnetic stir bar and Fe_3O_4 nanoparticles (0.05 mmol, 5 mol %) in air, aldehyde (0.5 mmol), amine (0.6 mmol), and alkyne (0.75 mmol) were added. The tube was then stoppered. The reaction mixture was stirred at 80 °C (oil bath temperature) for 24 h. The Fe_3O_4 nanoparticles were adsorbed on to the magnetic stirring bar when the stirring was stopped. After cooling to room temperature, the reaction solution was filtered through Celite in a pipette eluting with ethyl acetate. The volatile liquid was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (eluent: hexane–ethyl acetate = 15 : 1) to give the corresponding product. Fe_3O_4 nanoparticles were washed with ethyl acetate, air-dried and used directly for the next round of reactions without further purification.

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