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One-pot synthesis of magnetic silica supported copper catalyst has been described via *in situ* generated magnetic silica ($Fe_3O_4@SiO_2$); the catalyst can be used for the efficacious amination of aryl halides in aqueous medium under microwave irradiation.

Introduction

Amination of aryl halides is a very important transformation and a method of choice for the synthesis of fascinating motifs containing the N-aryl moiety;¹ they are widely present in many biologically important natural products and pharmaceuticals. The Buchwald-Hartwig amination using palladium catalyst has been well explored.² However, this method requires phosphine, N-heterocyclic carbenes, and many other complex organic ligands. The main limitation of this amination reaction is that these ligands are often air-sensitive, many of them are expensive and often require longer reaction times.¹⁻² In recent years, there has been significant progress in the discovery of copper-catalyzed coupling reaction of aryl halides with amines,³ a pathway that has been highly dependent on the use of organic ligands.⁴ Although these ligands have been very important for accelerating copper-catalyzed coupling of aryl halides with amines, none of them has displayed general efficiency for promoting coppercatalyzed N-arylation.

Thus, the development of a mild and efficient method for the amination of aryl halides under eco-friendly conditions for the synthesis of arylamines that can circumvent the extravagant use of stoichiometric reagents is highly desirable. Magnetic nanoparticles have emerged as a robust, high-surface-area heterogeneous catalyst support.⁵ Magnetic recoverability, which eliminates the necessity of catalyst filtration after completion of the reaction is an additional positive attribute of these materials⁶ compared to most of the heterogeneous catalysts deployed. These catalysts work well but suffer from following drawbacks a) synthesis of the catalyst is an elaborate and tedious procedure which involves three steps, i) synthesis of nano ferrite, ii) post-synthetic modification via anchoring of ligand which may be toxic and, iii) immobilization of catalytically active metal. To overcome these drawbacks and to avoid the use of toxic ligands and reagents we have developed a onestep procedure for the synthesis of magnetic silica supported CuSO₄ as a magnetically retrievable catalyst and have demonstrated its application for the amination of aryl halides in a benign aqueous media, which circumvents the use of organic solvents.

Results and discussion

The first step in the accomplishment of this goal was the easy synthesis of magnetic silica supported copper catalyst (Scheme 1) by sequential addition of reagents in one-pot. The magnetic nano ferrite (Fe_3O_4) was generated in-situ via hydrolysis method by stirring the solution of $FeSO_4 \cdot 7H_2O$ and $Fe_2(SO_4)_3$ in water in (1:1) ratio at pH 10 (adjusted using (25 %) ammonia (NH₃) solution) followed by heating in water bath at 50 °C for 1 h. The reaction mixture was cooled down to room temperature and tetraethyl orthosilicate (TEOS) was added to this solution with vigorous stirring which was continued for 18 h at ambient conditions. The supernatant liquid was decanted, fresh water added and to this solution, CuSO₄ was added and stirring was continued for another 24 h (Scheme 1).



Scheme 1 Synthesis of Magnetic silica supported copper catalyst



Figure 1a . TEM image of Fe₃O₄@SiO₂Cu

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Magnetic silica supported CuSO₄ catalyst was separated using an external magnet, washed with water followed by acetone and dried under vacuum at 50 °C for 8 hours. The catalyst was characterized by transmission electron microscopy (TEM) (Fig 1a) and X-ray diffraction (XRD) (Fig 1b) which confirmed the formation of single-phase silica coated Fe₃O₄ nanoparticles Fe₃O₄@SiO₂Cu, with spherical morphology and a size range of 5-30 nm. The weight percentage of Cu was found to be 4.92% by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis.

The application of magnetic silica supported copper catalyst was then demonstrated in a heterogeneous catalyzed amination of aryl

halides in aqueous medium as a benign solvent under microwave (MW) irradiation conditions (**Scheme 2**). Use of MW-assisted chemistry is due to the efficiency of the interaction of polar nano catalysts as well as water molecules with microwaves and the reaction mixture is rapidly heated to requisite temperatures under MW irradiation with a precise control of the reaction temperature.⁷ Initially, experiments were performed to optimize the reaction conditions for the amination of 4-nitro bromobenzene by pyrrolidine in aqueous medium (Table 1).



Scheme 2 Amination of 4-nitro bromobenzene using $Fe_3O_4@SiO_2Cu$

 Table 1 optimization of reaction condition

Entry	Catalyst	Time	Temperature (°C)	Yield
1 ^a	Fe ₃ O ₄	24 h	100	-
2 ^b	Fe ₃ O ₄	60 min	100	-
3 ^b	Fe ₃ O ₄	60 min	150	-
4 ^b	Fe ₃ O ₄ @SiO ₂ Cu	60 min	100	96%
5 ^a	Fe ₃ O ₄ @SiO ₂ Cu	24 h	100	traces

a) Reactions were performed under conventional heating; b) Reaction were performed under MW irradiation

First, the reaction was conducted using nanoferrites $nano-Fe_3O_4$. The amination reaction did not proceed under conventional heating (24 h, 100 °C, Table 1, entry 1), or under MW irradiation at 100 °C or at 150 °C, even after 60 min of MW exposure (Table 1, entries 2-3). The magnetic silica supported copper catalyst $Fe_3O_4@SiO_2Cu$ was then tested for the amination of 4-nitro bromobenzene with pyrrolidine at 100 °C using MW and conventional heating. Under conventional heating, it gives trace amount of product whereas MW exposure for 1 h at 100 °C leads to the nearly quantitative conversion of 4-nitro bromobenzene to corresponding aryl amines (Table 1, entry 4). The variation in base did not influence the outcome of the reaction; results with Cs₂CO₃ were similar to those obtained using K₂CO₃ Using the above optimized conditions, the scope of magnetic silica supported copper catalyst Fe₃O₄@SiO₂Cu was then explored for the amination of a variety of aryl halides (Table 2). The catalyst displayed high activity for amination of aryl bromide and iodide using primary, secondary, cyclic, and acyclic amines in pure water (Table 2 entry1-17). The rates were barely influenced by the electronic effects of the substituent's on the aromatic ring of the aryl halides (Table 2 entry 1-15). The cyclic (Table 2, entry1-10 and entry 16-17) and acyclic amines (Table 2, entry 11-15) do not show any difference in reactivity. Primary and secondary amines react efficiently. It was interesting to observe that 1- bromo-4-iodo benzene can be selectively converted to corresponding bromo aryl amines (Table 2 entry 16) after 60 min exposure to MW at 100 °C with 1 equivalent of pyrrolidine. The reaction of aryl halides bearing both halide (Br) and boronic acid functional groups with amines leads to the formation of corresponding aryl amines along with the removal of boronic acids moiety (Table 2, entry 17). The aryl chlorides were not reactive enough to be converted into the corresponding amines, however. We have not observed any product when similar reaction was performed with benzene chloride and pyrrolidine (Table 2 entry 18). TON and TOF of the reactions (Table 2) clearly indicates that the method will be very useful for aryl amine synthesis.

The lifetime of the catalyst and its level of reusability are important considerations in terms of practical applications. To clarify this issue, a set of experiments for the amination of 4-nitro-1bromobenzene with pyrrolidine using Fe_3O_4 ($@SiO_2Cu$ catalyst were established. After the completion of the first reaction to afford the corresponding aryl amine, the catalyst was recovered magnetically, washed with acetone, and dried at 50 °C. A new reaction was then performed with fresh 4-nitro-1-bromobenzene under the similar condition. The magnetic silica supported copper catalyst Fe₃O₄@SiO₂Cu could be reused at least three times without any change in the activity (ESI, Table 1). Metal leaching was studied by ICP-AES analysis of the catalyst before and after the three reactions. The Cu concentration was found to be 4. 92 % before the reaction and 4.87 % after the reaction. The TEM image of the catalyst taken after the third cycle of the reaction did not show any significant change in the morphology or in the size of the catalyst nanoparticles (ESI, Fig. 1), which indicates the retention of the catalytic activity after recycling. No Cu metal was detected in the reaction solvent (water) after completion of the reaction. This confirms the fact that nano magnetic silica held the copper catalyst very tightly, minimizing the deterioration of the catalyst and thus metal leaching and facilitating efficient catalyst recycling.



a) Reaction condition: 1) Fe₃O₄@SiO₂Cu (25 mg), amine (1.1mmol), K₂CO₃ (2 mmol), Water (4 mL), MW 100 °C. 60 min: b) Isolated vield: c) TON/TOF calculated based on 10 mmol reaction, reaction time 4 h

Conclusion

A novel one-step procedure for the synthesis of magnetic silicasupported copper catalyst has been developed, which can be readily prepared in gram quantities in aqueous media. It catalyzed the amination of aryl halides and the desired reactions proceeded smoothly to deliver the corresponding aryl amines in very good yields. Because of the magnetic nature of the catalyst, it can be separated using an external magnet, which eliminates the requirement of catalyst filtration after completion of the reaction, which is an additional attribute of the catalyst.

Experimental section

Synthesis of magnetic silica supported ruthenium hydroxide nanoparticles

 $FeSO_4$ ·7H₂O (1.39 g) and $Fe_2(SO_4)_3$ (2.0 g) were dissolved in 100 mL water in a 250 mL beaker. Ammonia solution (25%) was added slowly to adjust the pH of the solution to 10. The reaction mixture was then continually stirred for 1 h at 50 °C. The reaction mixture was cooled down to room temperature, tetraethyl orthosilicate (TEOS, 10 mL) was added and vigorous stirring was continued for 18 h at ambient conditions. The supernatant liquid was decanted, fresh water added and to this solution, CuSO₄ (400 mg) was added and stirring was continued for another 24 h (Scheme 1). Magnetic silica supported CuSO₄ catalyst was separated using an external

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magnet, washed with water followed by acetone and dried under vacuum at 50 °C for 8 hours. Catalyst characterization by X-ray diffraction (XRD) (Fig 1a MS) and transmission electron microscopy (TEM) (Fig 1b, MS) confirms the formation of singlephase silica coated Fe₃O₄ nanoparticles Fe₃O₄@SiO₂Cu, with spherical morphology and a size range of 5-30 nm. The weight percentage of Cu was found to be 4.92% by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis.

Amination of aryl halides

Aryl halide (1.0 mmol), Amine (1.1 mmol), K_2CO_3 (2.0 mmol) and Fe_3O_4 @SiO₂Cu (25 mg) were placed in a crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. Water (4 mL) was added to the reaction mixture. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 100 °C (temperature monitored by a built-in infrared sensor), 100 Watts for 60-90 min. After completion of the reaction, the catalyst was easily removed from the reaction mixture using an external magnet. Product were extracted using ethyl acetate, dry over sodium sulfate, concentrated under reduced pressure and purified using column chromatography.

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Notes and References

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Electronic supplementary information (ESI) available:

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