# Synthesis of primary amines via alkylation of ammonia with alcohols using the magnetic nano-catalyst NCM@EDTA/Cu(II)

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**Abstract:** This article introduces the utilization of $Fe_3O_4@SiO_2@CS@EDTA/Cu(II)$ (NCM@ EDTA/Cu(II) core-shell nanoparticles as a magnetically assisted catalyst. These nanoparticles effectively transform various aliphatic and aromatic alcohols, featuring both electron-donating and electron-withdrawing groups, into primary amine derivatives using ammonia in an eco-friendly manner. The research focused on optimizing reaction conditions, encompassing variables such as temperature, reaction time, and catalyst quantity, to establish the most favorable parameters. Optimal results were achieved employing 0.3 mmol of catalyst per 1 mmol of alcohol derivatives under reflux conditions for 1 hour. The reaction mechanism involves alcohol conversion to a carbonyl compound, subsequent imine formation between the amine and carbonyl, followed by imine reduction. Findings suggest that benzylic alcohol especially with electron-donating groups enhance the reaction rate, whereas electron-withdrawing groups, such as nitro, diminish overall yield. Moreover, the reaction demonstrates notable efficiency, bolstered by the easy catalyst retrieval via an external magnetic field, its stability, and reusability, which collectively underscore its significance in both organic chemistry and industrial settings.

**Keywords:** Amination, Magnetic nanocatalyst, Core-shell nanoparticle, Ammonia, Heterogeneous catalyst.

## Introduction

Amines play pivotal roles in both bulk and fine chemical industries, facilitating the production of polymers, dyes, pharmaceuticals, and agrochemicals[1]. These compounds, are versatile building blocks with the capability to generate a broad spectrum of organic molecules[2]. The formation of carbon-amine bonds represents a fundamental concept in organic chemistry, holding profound importance in construction and synthesis, especially serving as diverse precursors for synthesizing biologically active compounds[3].

In light of their significance, a plethora of methodologies have emerged, including Hofmann alkylation[4], the Buchwald-Hartwig reaction[5], the Ullmann reaction[6], hydroamination[7], hydrogen transfer processes[8],

amination or hydroamination of alkenes and alkynes[9], as well as the reduction of nitriles and nitro compounds[10], and the production of amines through the reduction of carbonyl compounds[11]. Among these methods, the catalytic amination of alcohols with ammonia for the production of lower alkyl amines emerges as an industrially significant process[12]. Various synthesis methods have been introduced to address this significance. One interesting approach in this realm is the amination of alcohols using intermediate metal catalysts[13]. These alcohols, upon losing hydrogen, generate a carbonyl intermediate, which, in the presence of amines, undergoes transformation into an imine or iminium species. Subsequently, in the presence of water molecules, the carbonyl intermediate undergoes further transformation into a new amine with a newly attached alkyl group.

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The development of efficient and practical catalytic systems for alcohol amination represents a significant advancement towards greener synthetic processes in the production of various organic molecules and biologically active compounds[13]. Recent catalysts utilized in this reaction include copper-aluminum hydrotalcite NiCuFeO$_x$[14], Ru$_3$(CO)$_{12/}$ CataCXium PCy[15], Fe$_3$O$_4$@SiO$_2$ shell-coated APTES/AEAPS,[16] (CuAl-HT)/K$_2$CO$_3$, NCS@POCl$_{2-x}$/Cu (II)[17-19], NCM@EDTA/Cu(II)[20], CuO-NiO/γ-Al$_2$O$_3$[21], Cu(OH)$_x$/TiO$_2$[22], Cu(OH)$_x$/Al$_2$O$_3$[22], mesoporous TiO$_2$-Fe$_2$O$_3$[23], Ru/ZrO$_2$[11] and Ni/Al$_2$O$_3$[24].

The Fe$_3$O$_4$@SiO$_2$@CS@EDTA nanocomposite is a unique and advanced catalyst with a core-shell structure due to the inclusion of intermediate metal. This composite goes through a sequential coating process, starting with iron oxide nanoparticles embedded in silica, followed by chitosan, and finally by EDTA. Our research team introduced and improved this catalyst synthesis[25]. Its significance features lie in its distinct, such as easy separation from the solution using a magnetic field and stability in the reaction environment due to the attachment of functional groups through chemical bonds. To extend the application of this catalyst, we conducted a synthesis involving the amination of alcohols with the assistance of NCM@EDTA in the presence of Cu(II) ions as a catalyst and ammonia as reagent. Using a catalyst in alcohol amination provide numerous advantages, including recyclability, easy separation from the reaction medium with an external magnetic field, simple synthesis, and exceptional selectivity. These qualities make it attractive to both researchers and industries alike.

**Results and Discussion**

Initially, we explored methods to enhance primary amines by combining benzyl alcohol with ammonia and using a specific catalyst known as NCM@EDTA/Cu(II)[20, 25]. We experimented with various parameters, including adding a base, adjusting the reaction time, using a reducing agent, controlling the temperature, and varying the amount of catalyst used. Our results showed that the addition of a chemical called NaBH$_4$ significantly improved the reaction (Table 1, entry 4). Even without NaBH$_4$, the reaction still occurred but just took longer. Presence of K$_2$CO$_3$ has no effect of reaction due to presence NH$_3$ as base and reagent. Optimal results were achieved when using 0.3 mmol of NCM@EDTA/Cu(II) catalyst for every 1 mmol of benzyl alcohol, maintaining the temperature at 80 °C, allowing for a 10 hour reflux reaction, and including 0.1 mmol of NaBH$_4$. This combination resulted in a 90% conversion rate (Table 1, Entry 6).

**Table 1.** Optimizing of benzyl alcohol (1 mmol) to benzylamine conversion in the presence of NCM@EDTA-Cu(II) catalyst.



| Entry | Catalyst (mmol) | Catalyst (type) | Base/ reducing agent | Time(h) | Yield (%) |
|-------|-----------------|-----------------|----------------------|---------|-----------|
| 1 | 0.4 | NCM@EDTA | - | 24 | - |
| 2 | 1 | NCM@EDTA/Cu(II) | - | 24 | 70 |
| 3 | 1 | NCM@EDTA/Cu(II) | K$_2$CO$_3$ | 10 | 70 |
| 4 | 1 | NCM@EDTA/Cu(II) | NaBH$_4$ | 2 | 100 |
| 5 | 0.5 | NCM@EDTA/Cu(II) | NaBH$_4$ | 3 | 92 |
| 6 | 0.3 | NCM@EDTA/Cu(II) | NaBH$_4$ | 3 | 90 |

The study investigated reactions involving benzyl alcohol derivatives with various functional groups, including nitro and methoxy, as outlined in Table 2. It was observed that electron-donating groups on the benzyl ring accelerated the reaction, while electron-withdrawing groups, such as nitro, slowed it down, requiring more time. This disparity arises from the influence of these functional groups on the intermediate stages of the reaction, favoring oxidation with electron-donating groups over electron-withdrawing ones.

Additionally, the presence of electron-withdrawing groups led to a decrease in overall yield (Table 2, entries 3 and 4). In comparisons, aliphatic alcohols displayed a significant decrease in both conversion rate and overall yield when compared to benzyl alcohols (Table 2, entry 5). This can be attributed to the greater complexity involved in forming carbonyl intermediates from aliphatic alcohols.

**Table 2**: Conversion of different alcohol structures to primary amines with ammonia using the NCM@EDTA/Cu(II) catalyst.

| Entry | substrate | Product | Yield (%) |
|---|---|---|---|
| 1 | Benzyl alcohol | Benzyl amine | 91 |
| 2 | *p*-methyl benzyl alcohol | *p*-methyl benzyl amine | 93 |
| 3 | *p*-methoxy benzyl alcohol | *p*-methoxy benzyl amine | 96 |
| 4 | *p*-nitro benzyl alcohol | *p*-nitro benzyl amine | 81 |
| 5 | *1*-octanol | *1*-octane amine | 74 |

While this method requires higher reaction temperatures and larger amounts of amines the use of the cost-effective and heterogeneous catalyst NCM@EDTA/Cu(II), offers the advantage of easy separation in the presence of an external magnetic field as opposed to more expensive and non-reusable homogeneous catalysts. This demonstrates the versatility of the process in converting various aliphatic and benzylic alcohols containing both electron-donating and electron-withdrawing groups into amines.

The FESEM image of NCM@EDTA, depicted in Figure 1, highlights its distinctive spherical nanocomposite structure. This structural characteristic plays a crucial role in determining the catalyst's properties and performance in various chemical reactions.
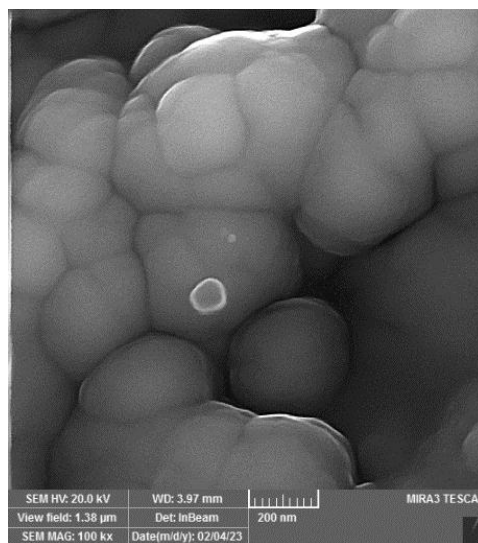


**Figure 1**. FESEM image of NCM@EDTA nanocomposite

For the suggestion of a mechanism, the carboxylate groups present in the structure of EDTA inside the catalyst appear to be capable of

rapidly forming a complex with copper (II) ions, creating the catalytic ensemble NCM@EDTA/Cu(II). This, in turn, facilitates the conversion of copper (II) to copper (I) and vice versa, easily achievable within the framework of the NCM@EDTA catalyst in the presence of $NaBH_4$. Therefore, it is anticipated that the oxidation step likely occurs through the formation of an alkoxide, involving the dissociation of a proton from the alcohol in the presence of ammonia, and its coordination with the copper center in NCM@EDTA/Cu(II). Copper alkoxy intermediates are then converted to amine products, demonstrating a dynamic process that involves the reversible transformation of copper(I) to copper (II) facilitated by the structure of the catalyst.this mechanism was shown in Figure 2.
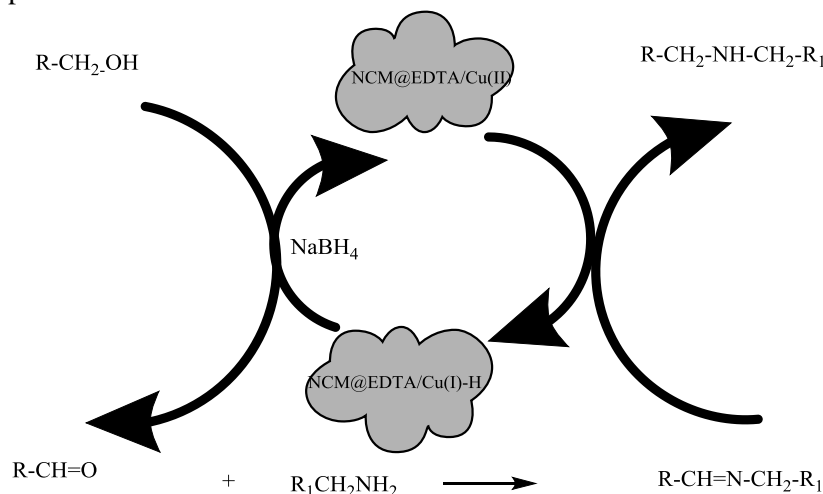


**Figure 2.** Proposed mechanism for the reaction of alcohols with amines using the NCM@EDTA/Cu(II) catalyst

The NCM@EDTA/Cu(II) catalyst can be easily separated from the reaction mixture using an external magnetic field. After extraction, the catalyst is sequentially washed with acetone, ethanol, and water, then dried at 65°C. The recovered catalyst is then used in multiple cycles to evaluate its reusability and efficiency, as detailed in Table 3.

**Conclusion**

In conclusion, the NCM@EDTA/Cu(II) catalyst proves to be effective in the alkylation of ammonia with alcohols, with optimal conditions resulting in a high conversion yield. This catalytic system shows great promise in the field of organic chemistry, providing advantages such as easy catalyst separation using an external magnetic field, stability in the reaction environment, and simple recyclability.

**Experimental Section**

All materials were procured from Merck company. The catalyst preparation procedure for NCM@EDTA-Cu(II) follows the methodology previously documented[25]. The compounds synthesized in this study are well-established, and their identities are confirmed through known characterization techniques.

***Alkylation of ammonia with alcohol derivatives using NCM@EDTA/Cu(II) catalyst***

In the amination of alcohols process, a mixture containing NCM@EDTA/Cu(II) catalyst (0.8 g, 0.3 mmol), the corresponding alcohol (1 mmol), and ammonia (3 mmol) is combined in a round-bottom flask with 10 ml of acetonitrile as the solvent. A solution of $NaBH_4$ (0.1 M) is then added drop by drop to the mixture and heated, subjected to reflux under an argon gas atmosphere at 80°C for a duration of 3 to 4 hours. The conversion and product yield are then assessed using Thin-layer chromatography (TLC) before undergoing a final purification step. The

NMR spectrum of the obtained product is compared to that of a standard sample for further characterization and validation.

**Table 3**. Catalyst recovery in the reaction of methoxybenzyl alcohol and ammonia
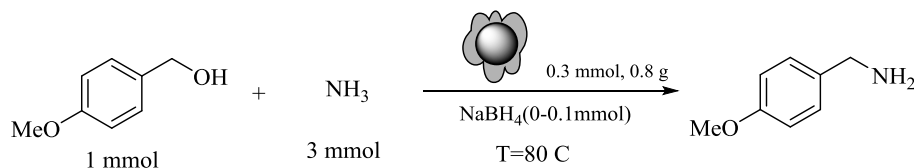


| Entry | Recovery Steps | Yield (%) |
|-------|----------------|-----------|
| 1 | One cycle | 96 |
| 2 | Two cycle | 94 |
| 3 | Three cycle | 90 |

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