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CuMgAl Hydrotalcite as an Efficient Bifunctional Catalyst for the Cross-Dehydrogenative C–C Coupling Reactions under Mild Conditions

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Graphical abstract



Highlights

- CuMgAl LDH acts as an efficient heterogeneous catalyst for the CDC reaction.
- Efficient heterogeneous catalyst for the CDC reaction between N-aryltetrahydroisoquinolines and various C-H bonds.
- NH₃·H₂O copreciptated CuMgAl hydrotalcite exhibites "acidic" surface property.
- Redox-acidity dual function has been observed in the aerobic CDC reaction.
- A probable reaction mechanism comprising an iminium ion intermediate was proposed.

Abstract: CuMgAl layered double hydroxide compounds (CuMgAl-LDHs) have been synthesized, characterized and investigated in the aerobic CDC reactions. The results indicated that NH₃·H₂O

coprecipitated CuMgAl LDH (N-CuMgAl-LDH) was able to efficiently accelerate the CDC reactions between the α -C_{sp3}–H of *N*-aryltetrahydroisoquinolines and nucleophiles. A wide scope of *N*-aryltetrahydroisoquinoline analogues and nucleophiles with different C–H bonds (C_{sp3}–H, C_{sp2}–H and C_{sp}–H) could be tolerated by the N-CuMgAl-LDH system. Compared with the sample using Na₂CO₃ as the precipitant (C-CuMgAl-LDH), N-CuMgAl-LDH showed higher catalytic activity, which probably was due to its higher surface acidity. Dual function of redox and acidity for the N-CuMgAl-LDH catalyst has been observed in the CDC reaction. According to the obtained catalytic results, kinetic isotope effect experiment and XPS analysis, iminium ion was proposed as the key intermediate, made possible by the cycle of Cu²⁺ and Cu⁺ under the aerobic conditions.

Keywords: CuMgAl hydrotalcite; cross-dehydrogenative-coupling reaction; tetrahydroquinoline; bifunctional catalysis; surface acidity

1. Introduction

Cross-dehydrogenative-coupling (CDC) reaction has been a vital tool for constructing C–C bonds, which avoids prefunctionalization of the substrates and provides an environmentally friendly synthetic process with high atom economy [1,2]. In spite of the significant progress made in homogeneous catalytic systems derived from metal salts or complexes of Cu [3-11], Co [12], Fe [13-16], Ru [17-19], Au [20] and Rh [21, 22], etc, and in some metal-free systems [23-27], it is hard for homogeneous systems to achieve sustainability and cost-effectiveness. Actually, some heterogeneous catalytic systems, including nanoporous gold [28], magnetic nanoparticle-immobilized bipy-gold(III) complex [29], graphene-supported RuO₂ [30] and some photocatalyzed systems [31-36] have been described for the transformation. However, most of these catalysts were based on noble metals or required complicated preparation methods, and sometimes peroxides or additives were needed. Although SBA-15-support iron terpyridine [37] and CuFe₂O₄ nanoparticles [38] have been developed for the CDC reaction, TBHP (*tert*-butyl hydroperoxide) or benzoquinone analogues were required as additives in some cases. Therefore, developing efficient and recyclable catalyst originated from available materials using molecular oxygen without any additives for CDC reaction is still highly desirable. Furthermore, all the above heterogeneous

catalytic systems have only been explored for limited types of substrate.

According to the proposed reaction path for the CDC reaction of *N*-aryltetrahydroisoquinolines [3, 33, 34], it is generally believed that iminium cation is firstly formed via oxidative dehydrogenation, and a nucleophile attacks the intermediate to afford the coupled products. Copper salts and complexes have been most extensively studied as catalysts for the CDC reactions, and the most notable examples are CuBr/TBHP and CuCl₂/O₂, developed by Li's [2,10] and Klussmann's groups [3], respectively. Copper species have been considered to be effective for the first reaction step and formation of iminium cation [3-11], and base or acid is suggested to be helpful for the following nucleophilic reaction. On the other hand, layered hydroxide compounds (LDHs), have been widely applied as catalyst in various reactions for its adjustability of metallic composition and surface physicochemical properties [39-42]. In our recent research, LDHs with different compositions have been found effective in the catalytic dehydrogenation of alcohols [43-46] and *N*-heterocycles [47]. On the basis of the above analysis and our obtained results, we envisioned that introducing Cu into LDHs structure might provide an efficient heterogeneous catalyst for the CDC reaction between *N*-aryltetrahydroisoquinolines and various C–H bonds.

In the present study, CuMgAl LDHs were prepared respectively with NH₃·H₂O and Na₂CO₃ as the precipitant, which would lead to different interlayer anions and varied surface properties. Although these are the common reagents in preparing LDHs, rare study has been reported for the effect on the catalytic activity in organic transformation. The prepared samples were then characterized and investigated in the catalytic aerobic CDC reaction without any additives. Good results have been obtained for the present catalytic system, and the bifunctional roles of the catalyst and possible reaction pathway have also been discussed according to a series of controlled experiments.

2. Experimental

2.1 Chemicals

All the chemicals used were obtained from commercial sources.

N-phenyl-1,2,3,4-tetrahydroisoquinolines were synthesized from corresponding tetrahydroisoquinolines and aryl halides according to the reported method [48]. 1-Deutero-2-phenyl-1,2,3,4- tetrahydroisoquinoline (**1a-d**₁) was synthesized according to the reported method [3], and the purity of **1a-d**₁ was 89% according to ¹HNMR analysis.

2.2 Synthesis of CuMgAl LDHs

Taking N-CuMgAl-LDH as an example, solution (I) was prepared by dissolving Cu(NO₃)₂·6H₂O (0.05 mol), Mg(NO₃)₂·6H₂O (0.05 mol) and Al(NO₃)₃·6H₂O (0.05 mol) in 150 mL deionized water. The solution (II) and (III) were prepared by dissolving NaOH (0.04 mol) and NH₃·H₂O ($25 \sim 28\%$, 20.0 g) in 100 mL deionized water, respectively. Next, the solution (I) and (II) were added dropwise into solution (III) with stirring (400 r/min) under 60 °C and a pH=10±0.2 was maintained. The suspension was stirred for another 3 h. After being digested at 40 °C for 14 h, the obtained precipitate was washed to neutrality. The powdery N-CuMgAl-LDH sample was obtained after being dried at 70 °C for 12 h. C-CuMgAl-LDH sample was prepared through the same procedure by replacing the NH₃·H₂O with Na₂CO₃. Mg₂Al-LDH was obtained by similar procedure.

2.3 Characterization of CuMgAl LDHs

The structure and morphology of samples were confirmed by Powder X-ray diffraction (XRD, Rigaku D/max 2500 PC X-ray diffractometer), scanning electron microscopy (SEM, JSM-6010plus/LV scanning electron microscope) and Transmission electron microscope (TEM, JEM 2100). The contents of Cu, Mg and Al were obtained via inductively coupled plasma analysis (ICP) in a Varian Vista-AX device. The FTIR spectra were analyzed on a Nicolet PROTÉGÉ 460 FTIR spectrometer. X-ray photoelectron spectroscopy (XPS) was measured on a Thermo Scientific ESCALAB 250Xi instrument. ESI-MS analysis for the intermediate was performed on a Finnigan TSQ Quantum Mass Spectrometer. Porosity and surface area studies were conducted on a micromeritics ASAP2010C apparatus. The surface area was calculated using the BET method and the pore size distributions were deduced from the adsorption branches of the isotherms using the BJH method.

Temperature programmed desorption of ammonia (NH₃-TPD) was conducted on an AutoChem II 2920 TPR/TPD instrument equipped with mass detector (MS). The samples (120 mg) were first pretreated for 2 h at 150 °C with a carrier gas He flow-rate of 50 mL/min. Then ammonia was adsorbed at 50 °C for 1 h using 10% NH₃/He with a flow-rate of 50 mL/min. He flow (50 mL/min) was purged for 1h to remove the excess ammonia. Finally, the temperature was increased linearly at a rate of 10 °C/min from 50 °C until all the ammonia was desorbed. The desorbed ammonia was detected by a mass detector,

Infrared spectra of pyridine adsorption (Py-IR) was recorded to determine the type and ratio of acid

sites with NICOLET 6700 spectrometer with a wedge attenuator in the reference beam. Selfsupporting discs of samples were made by pressing 100 mg of dry powder at 10^8 N/m² in a 25 mm diameter die. The samples were outgassed for 1 h at 100 °C. Then pyridine (1.5 mmHg) was adsorbed (0.5 h, r.t.), its excess was eliminated by evacuation (0.5 h, r.t.) and the spectrum was recorded. Pyridine was then desorbed for 1 h at 150 °C and spectra recorded.

2.4 CDC reaction between N-phenyl-1,2,3,4-tetrahydroisoquinoline and nitromethane

Typically, a mixture of *N*-phenyl-1,2,3,4-tetrahydroquinoline (**1a**, 0.50 mmol), nitromethane (**2a**, 3.0 mmol), N-CuMgAl-LDH (0.2 g), 1, 4-dioxane (2 mL) and 1,4-dinitrobenzene (0.1 mmol) in a Schlenk reactor was stirred at 80 °C under oxygen atmosphere. TLC was used to monitor the CDC reaction, and the product **3aa** was analyzed through a NMR spectrometer (400 MHz). After the finish, the reaction mixture was cooled and filtrated. After being washed with ethyl acetate and dried, the obtained catalyst was recycled in a similar reaction. The conversion of **1a** and the selectivity of CDC product were calculated according to the ¹HNMR analysis (using 1,4-dinitrobenzene as the internal standard reference). The turnover frequency (TOF) value was calculated according to the Cu content on the surface of catalyst with a <10% conversion. The surface Cu amount was determined by the Langmuir adsorption isotherms of phenol on the catalyst [49] (Fig. S1). The parameters are defined as follows:

Conversion (%) =
$$\frac{\text{moles of } 1a \text{ converted}}{\text{moles of } 1a \text{ in feed}} \times 100\%$$

Selectivity (%) = $\frac{\text{moles of } 3aa \text{ formed}}{\text{moles of } 1a \text{ converted}} \times 100\%$

TOF
$$(h^{-1}) = \frac{\text{moles of } \mathbf{1a} \text{ converted}}{\text{moles of surface active sites } \times \text{ reaction time}}$$

2.5 Kinetic isotope effect studies

The reactions were performed as described above except for the use of $1a-d_1$ instead of 1a. When $1a-d_1$ was completely converted, KIE values k_H/k_D were calculated based on the ¹H-NMR analysis. For the calculation of KIE values, it was taken into account that substrate $1a-d_1$ was only 89% pure, containing 11% of the nondeuterated 1a.

3. Results and discussion

3.1 Characterization of CuMgAl LDHs

Two methods have been applied to prepare CuMgAl LDHs by using NH₃·H₂O (N-CuMgAl-LDH) and Na₂CO₃ (C-CuMgAl-LDH) as the precipitant, respectively. For the two samples, the characteristic hydrotalcite reflections can be obviously found from the XRD patterns depicted in Fig. 1. The (003) and (006) planes can be found at 11° and 22°, respectively; and the broad peaks between 33~47° are related to the (012), (015) and (019) planes [50,51]. The distinguishable reflections between 60~63° are related to planes (110) and (113). The peak shape for the C-CuMgAl-LDH indicates its well ordering of both the anions and the cations [52, 53], while N-CuMgAl-LDH exhibits lower crystallinity. The diffraction sites for (003), (006) and (018) are varied for the two samples. The lattice parameters "c" corresponding to the sum of the thickness of a brucite-like layer and an interlayer can be calculated from (003) reflection. The "c" parameter increased from 7.609 to 8.874 when NH₃·H₂O was used as the precipitant instead of NaCO₃, indicating the main interlayer anions were NO₃⁻ and CO₃²⁻ respectively for N-CuMgAl-LDH and C-CuMgAl-LDH samples [54].

Figure 1

The DR UV-Vis results (Fig. S2) of the two samples were in accordance to the previous reports [52, 55], two main bands around 250 and 720 nm accompanied. The first band can be attributed to the $O^{2-} \rightarrow Cu^{2+}$ ligand to metal charge transfer transition, and the other broad band is related to d–d transitions of Cu^{2+} ions in the distorted octahedron. Concerning the FTIR spectra (Fig. S3), the two samples displayed similar profiles at the band around 3456 cm⁻¹ and 1637 cm⁻¹, which is generally related to the OH stretching vibration of layer hydroxyl groups and interlayer water molecules [52, 56]. The smaller half-width of the peak at 3456 cm⁻¹ for the C-CuMgAl-LDH than for the N-CuMgAl-LDH sample reflects a more ordered cation distribution in the former, in consistent with the XRD analysis [57]. The band at 1384 cm⁻¹ in N-CuMgAl-LDH is attributed to the vibration of NO₃⁻ groups and a shoulder peak at 1366 cm⁻¹ is linked to carbonate traces [54, 57]. The strong band at 1366 cm⁻¹ is described to the asymmetric stretching mode of the carbonate species, indicating the intercalated CO_3^{2-} in C-CuMgAl-LDH sample. The bands below 700 cm⁻¹ are assigned to metal oxygen modes in the hydrotalcite lattice [52]. The SEM and TEM micrographs (Fig. 2) show that the prepared CuMgAl LDHs with different precipitants were plate-like particle, further indicating the formation of hydrotalcites [58,59]. And the crystallinity for C-CuMgAl-LDH was obviously higher than N-CuMgAl-LDH.

Figure 2

XPS spectra were conducted to better verify the Cu species in the N-CuMgAl-LDH and C-CuMgAl-LDH samples. As illustrated in Fig. 3, the main peaks of Cu 2p3/2 for the N-CuMgAl-LDH and C-CuMgAl-LDH catalysts are both located at around 933.6 eV, indicating that Cu species exist in Cu(II) state in the two prepared samples [60, 61], in consistent with DR UV-Vis analysis.

Figure 3

Then, nitrogen sorption measurement was carried out to elucidate the textural parameters of the CuMgAl LDHs. The N₂ adsorption-desorption isotherm at –196 °C for the two samples are shown in Fig. S4. According to the IUPAC classification, the isotherms for the two samples are type IV, in consistent with the mesoporous structure of the materials. In contrast, the hysteresis loops are different, suggesting the different types of pore shapes, further verifying the different composition in the interlayers of the two samples. H2 type hysteresis loop was observed for the C-CuMgAl-LDH, while N-CuMgAl-LDH showed broad H3 type hysteresis loop, which might be attributed to aggregation of plate-like particles containing slit-shaped pores [62]. On the other hand, C-CuMgAl-LDH exhibited a BET surface area of 73.2 m²/g, markedly higher than that of N-CuMgAl-LDH (Table 1). The pore volume and average pore diameter of C-CuMgAl-LDH sample were all bigger than N-CuMgAl-LDH, which might be attributed to the lower crystallinity of N-CuMgAl-LDH.

Table 1

An interesting find is that suspension of N-CuMgAl-LDH sample in water showed slight acidic property (pH = 6.87, Table 1), while common hydrotalcites generally exhibit basicity [43, 63], just like the prepared C-CuMgAl-LDH (pH = 8.88, Table 1). The difference might be related to the interlayer anions of the two samples, as discussed for the XRD pattern and FTIR spectra. The NH₃-TPD was further introduced to elucidate the surface acidity of the two samples. To avoid the influence of pretreatment on the samples, the samples were pretreated at 150 °C to maintain the hydrotalcite structure; and MS detector was applied to avoid the influence of H₂O and CO₂ formed in the desorption procedure. From the Fig. 4, it is obvious that both of the two samples exhibited weak acidic sites around 110 °C and moderate acidic sites around 290 °C, while N-CuMgAl-LDH exhibited stronger acidic sites around 350 °C, indicating the stronger surface acidity

of N-CuMgAl-LDH than C-CuMgAl-LDH. Furthermore, the amount of the acidic site for

N-CuMgAl-LDH were markedly higher than that of C-CuMgAl-LDH, confirming the above speculation. **Figure 4**

Furthermore, Py-IR analysis was performed to study the contents of Brønsted and Lewis acid sites on the two catalysts (Fig. 5). Similar to the NH₃-TPD, the activation and desorption temperature were set at 100 °C and 150 °C, respectively, to avoid the destruction of hydrotalcite structure. The absorption peak located at 1445 cm⁻¹ is ascribed to pyridine molecules interacting with the Lewis acid sites, while 1540 cm⁻¹ for Brønsted acid sites [64]. The values summarized in Table 2 show that N-CuMgAl-LDH contained higher total amount of acid site than C-CuMgAl-LDH, in consistent with the NH₃-TPD analysis. Further, the amount of Lewis acidic site for N-CuMgAl-LDH is 37% higher than that of C-CuMgAl-LDH, while the value reaches 436% for the Brønsted acid sites (Table 2). The observations suggest that NH₃·H₂O as the precipitant has a greater impact on Brønsted acid sites on the surface of hydrotalcites.

Figure 5

Table 2

3.2 Catalytic activity of CuMgAl LDHs

3.2.1 Effect of the reaction conditions

CDC reaction between **1a** and **2a** was selected as the model reaction to study the effect of reaction conditions. The effect of solvent was firstly investigated. The results summarized in Table 3 show that toluene, DMSO and 1,4-dioxane gave higher conversions, while 1,4-dioxane provided a little higher selectivity to the corresponding product. The observations might be ascribed to the different polarity of these solvents, and 1,4-dioxane with moderate polarity gave relative higher activity and selectivity. Although methanol and propylene glycol monomethyl ether have been found efficient in some catalytic systems [8], they were not applicable in the present system. The results might be due to the fact that they are polar protic solvents, where propylene glycol monomethyl ether is supposed to have similar polarity with methanol. Although high conversion of **1a** was observed in water, the selectivity to the CDC product was quite low. The results should be due to its nucleophilic activity and the formation of oxygenation product (**4**) as the main by-product, which has been separated and identified by NMR spectra.

Table 3

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It can be observed that increasing the reaction temperature to 100 °C could not significantly improve the conversion of **1a** (Table 4, entry 2), but the selectivity to the coupled product decreased, which should be due to the overoxidation. Increasing the ratio of **2a/1a** from 1.5 to 6, the selectivity could be markedly improved to 97% (Table 4, entries 3-4), suggesting that increasement of the amount of nucleophile could suppress the side reaction. Prolonging the reaction time to 18 h led to a full conversion with an excellent 96% selectivity to the CDC product. Then, the CuMgAl LDH sample using the normally Na₂CO₃ precipitant was also conducted under the same conditions for comparison. However, the C-CuMgAl-LDH only gave 78% conversion and TOF with a comparable selectivity (Table 4, entry 6). The results might be not attributed to the morphology of the two catalysts, but probably due to the surface acidity. Higher amount of acidic site was observed for N-CuMgAl-LDH than C-CuMgAl-LDH, and nucleophilic reaction during the CDC transformation could be accelerated by acidic site [9]. Concerning the catalytic performance of the two samples and the distribution of the acidic sites from Py-IR analysis, Lewis acid site might play the key role in the reaction [65]. Boess, et al [3], have proposed that appropriate pH value for the reaction solution is required for the efficient CDC reaction, therefore, the higher catalytic performance for the N-CuMgAl-LDH was also probably related to its suitable surface property.

Table 4

3.2.2 Comparison with some other catalytic systems

To further elucidate the features of the catalytic system, the representative results over heterogeneous catalytic systems with oxygen have been collected from literatures. Most of the heterogeneous catalytic systems for the CDC reaction were based on noble metals. It can be seen from Table 5 that the present catalyst provided comparable catalytic performance with these systems (entries 2-5). CuFe₂O₄ (entry 6) and Fe₃O₄ nanoparticles (entry 7), developed by Li group [38, 66], could gave similar results but with higher temperature and longer reaction time. Nevertheless, DDQ (2,3-dicyano-5,6-dichlorobenzoquinone) was required when aromatic alkyne being used as the nucleophiles [38]. Furthermore, the synthesis procedures for some of these catalysts were very complicated, which would limit their application. Summary, N-CuMgAl-LDH has been developed as an efficient and simple heterogeneous catalytic system for the

CDC reaction between N-phenyl tetrahydroisoquinoline and nitromethane under mild conditions.

Table 5

3.2.3 The stability and recyclability of the N-CuMgAl-LDH

To elucidate the heterogeneity and stability of the N-CuMgAl-LDH, a hot filtration experiment has been conducted under the selected conditions. To make the discussion reasonable, it should be considered that the substrate can transform under the selected conditions even without catalyst. After 6 h (~35% conversion), the filtrate afforded only 7% additional conversion of **1a** for another 10 h under the same conditions (Fig. 6), suggesting that N-CuMgAl-LDH was a true heterogeneous catalyst. The ICP analysis of the reaction filtrate showed that the amount of Cu, Mg and Al ions were only 84×10^{-9} g/mL, 121×10^{-9} g/mL and 38×10^{-9} g/mL, respectively, implying that leaching of metals could be ignored. The recycled experiments showed that the N-CuMgAl-LDH could be reused at least three times with moderate loss of activity (Table 4, entries 5-7) and almost no reduction of the selectivity. XRD patterns for the reused catalyst suggests that the layered structure was basically preserved after several reuses (Fig. S5).

Figure 6

3.3 The scope of substrates

To test the scope of the N-CuMgAl-LDH catalyzed CDC reaction, various *N*-phenyltetrahydroisoquinoline derivatives were investigated (Table 6). The substrates with methyl or methoxyl at the *para*-site of *N*-phenyl ring could be well tolerated (**3ba** and **3ca**). The reduction of the yields might be due to the formation of the analogues of compound **4**. Delightedly, *N*-(4-tertbutylphenyl)-1,2,3,4-tetrahydroisoquinoline could give an excellent 89% isolated yield of the CDC product (**3da**). The longer reaction time might be due to the influence of the bulky tertbutyl group on the contact between the substrate and catalyst. In contrast, electron-withdrawing groups significantly slowed the reaction, and about 4 times of the reaction time were required when F, Cl or Br sits at the 4-site of the *N*-phenyl ring (**3ea**, **3fa** and **3ga**), suggesting that the electron density of N atom has a vital effect on the substrate's activity. Substituents located at the *ortho-* and *meta*-sites suppressed the CDC reaction, and only 30%-50% yields of the products could be obtained (**3ha**, **3ia**, **3ja**, **3ka** and **3la**). The reaction times were longer than that with the same substituents at *para*-site, further elucidating the effect of steric hindrance. Electronic effect was also observed in the cases of **3ma** and **3ma**. It is noteworthy that a good yield was

obtained for the 7-bromo-2-phenyl-1,2,3,4-tetrahydroisoquinoline, where the Br group was completely intact.

Table 6

Some other nucleophiles with C_{sp3}–H have been tested. To our delight, various nitroalkane could be tolerated by the present system (Table 7) (**3ab** and **3ac**), and slightly higher performance than the homogeneous CuBr/TBHP system [50,51] were obtained. The reactivity discernibly decreased as the carbon atoms increase, indicating the existence of steric effect. For the carbonyl compounds with α-C–H, 4-methyl-2-pentanone only gave 17% yield (**3ad**) for the steric hindrance and the lower nucleophilicity. In contrast, increased yields were obtained for cyclohexanone and acetophenone (**3ae** and **3af**). The substrate with a nitro group at the *para*-site of acetophenone could give significantly improved yield (**3ag**) for its easier formation of nucleophile. Trimethylsilyl cyanide and diethyl malonate were also investigated in the catalytic system, and moderate yields could be obtained (**3ah** and **3ai**).

Table 7

Finally, some nucleophiles with C_{sp2} -H or C_{sp} -H have also been examined. Indole and its derivatives were reacted with tetrahydroisoquinolines to produce the desired products with satisfied yields (Table 8). The reactions occurred selectively at the C3 position of indoles, consistent with the CuBr/TBHP system [10]. The indoles with electron-withdrawing or electron-donating groups could also be tolerated under the selected conditions. 1-Methylpyrrole could not give satisfied yield for its low nucleophilicity parameter (N= 5.85) (**3ao**) [3,67]. Similar result was found in case of benzofuran. Phenylacetylene with C_{sp} -H bond reacted well with **1a** under standard conditions, giving product **3ar** in good yield.

Table 8

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In summary, the present N-CuMgAl-LDH provides an efficient catalytic system for the aerobic CDC reactions. Compared with homogeneous catalytic systems based on copper salts or complexes, most substrates reacted under the selected conditions could give comparable or better yield of the target products. Although the yields were not satisfactory in some cases, the present heterogeneous catalyst would be more

practical for its heterogeneous feature.

3.4 The possible reaction pathway

To study the possible reaction pathway over N-CuMgAl-LDH, a series of controlled experiments have been conducted for comparison (Table 9). Only 45% selectivity could be observed with a lower conversion in the absence of catalyst, indicating that N-CuMgAl-LDH was crucial for the CDC reaction (entry 2). Under N₂ atmosphere, a lower conversion of **1a** was observed (entry 3), implying that molecular oxygen was not essential in the reaction, and the oxygen might be only involved in the reoxidation of reduced copper [3, 45, 68]. When air was applied instead of O₂, significantly reduced reactivity and selectivity of **3aa** were observed (entry 4). Mg₂Al-LDH could only give a 24% conversion of **1a** with a 62% selectivity (entry 5), and 75% of **1a** could be recovered after the reaction. These results implied that Cu species was essential for the reaction, and surface basicity might suppress the transformation, because Mg₂Al-LDH generally exhibits basicity. The observations further suggested the function of acidic site on the surface of catalyst. Only a 48% conversion with a 56% selectivity (entry 6) were obtained under CuMgAl hydroxide with mixed phases (Fig. S6), indicating that the hydrotalcite structure was crucial to improving the catalytic activity. The homogeneous CuCl₂ gave a full conversion of the substrate under the same conditions (entry 7), indicating that Cu species was effective for the oxidative transformation of **3a**. The quite lower selectivity to **3aa** than the reported result [3] might be due to the variation of reaction conditions.

Table 9

Radical scavenges (BHT (2,6-di-*tert*-butyl-4-methylphenol) and CCl₃Br) could significantly suppress the reaction (Table 9, entries 8 and 9), suggesting that radical might formed in the reaction. To demonstrate the possibility of the formation of iminium intermediate, which has been proposed as the key intermediate in the CDC reactions [3, 33, 34], the reaction was performed without a nucleophile, and the filtrate was analysed by MS with ESI ion source. The iminum could be obviously observed at 208.13 apart from the substrate peak (210.19) (Fig. S7). The MS2 spectra of the peak of 208.13 further verified the formation of iminium cation (**5**).

A KIE experiment was conducted to gain further information for the catalytic oxidative coupling reaction (Scheme 1). The monodeuterated 1,2,3,4-tetrahydroquinoline (**1a-d**₁) was introduced in the CDC reaction with **2a**, and a mixture of **3aa** and 1-deuterated **3aa-d**₁ were produced. When the substrate was

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completely converted, a primary KIE value k_H/k_D of 2.62 was calculated from the ratio of the signal intensity in the 1-position relative to reference signals. The observation was consistent with a fast SET rate-determining C–H bond cleavage [1].

Scheme 1

Finally, XPS analysis was performed to monitor the variations of surface copper valence during the reaction. The core fitting peaks of Cu $2p_{3/2}$ of the N-CuMgAl-LDH at different stages can be observed in Fig. 7. For the fresh sample, the Cu $2p_{3/2}$ spectrum can be fitted at 934.7 eV, which can be indexed to Cu²⁺ cations [69, 70]. After being used under N₂ atmosphere, the Cu $2p_{3/2}$ spectrum (Fig. 7B) shows a mixture valence of Cu²⁺ (934.8 eV) and Cu⁺ (932.9 eV) [69, 70], indicating transfer of electron to Cu²⁺. Most of the Cu⁺ was recovered after the normal catalytic process (Fig. 7C), indicating that the catalytic cycle has been finished. However, there was still some Cu⁺ remained, which might be responsible for the slight decrease of the catalytic activity. These XPS results implied that in the CDC reaction catalysed by N-CuMgAl-LDH contained multi-electron transfer between the Cu cations and the substrate.

Figure 7

On the basis of reported and preliminary mechanistic studies [3, 7], we propose a reaction pathway for the CDC reaction under N-CuMgAl-LDH (Scheme 2). The reaction is initiated by SET from N atom to Cu^{2+} , and the resulting amine radical species undergoes α -C–H abstraction to give an intermediate, which is stabilized by the N-Aryl group [71]. Finally, nucleophilic attack on the iminium intermediate **5** by nitromethane yields the coupled product **3aa**, where the surface acidic sites on the N-CuMgAl-LDH catalyst may play an important role.

Scheme 2

4. Conclusions

In summary, we have found that $NH_3 \cdot H_2O$ coprecipitated CuMgAl layered hydroxide presents redox-acidity dual functions in the CDC reactions, and provides an efficient heterogeneous catalytic system for the functionalization of α -C_{sp3}–H of *N*-aryl-1,2,3,4-tetrahydroquinoline via aerobic CDC reaction with various C–H bonds (C_{sp3}–H, C_{sp2}–H and C_{sp}–H). The catalytic system can tolerate various tetrahydroisoquinoline derivatives and nucleophiles, and present higher catalytic efficiency than reported heterogeneous catalytic systems. The surface acidity of the catalyst has been found crucial for the catalytic

performance in the CDC reactions. Based on a series of controlled experiments, XPS analysis and kinetic isotope effect experiment, a probable reaction pathway is suggested involving an iminium cation intermediate and a cycle between Cu²⁺ and Cu⁺. However, the effect of precipitant on the structure and property of the formed LDHs are needed to be further studied, which will provide new knowledge for its catalytic application.

Author contributions

Weiyou Zhou: Ideas, analysis of experimental data, writing the initial draft, revision
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Hui Wang: Analysis of experimental data
Zhenzhen Xia: Catalyst synthesis and characterization
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Zhong Zhang: Catalyst synthesis and characterization
Yuanjun Ma: Catalyst synthesis and catalytic experiments
Mingyang He: Oversight and leadership responsibility for the research activity planning and execution
Qun Chen: Design and direction of the project

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Figures and Tables

Fig. 1. The XRD patterns of the N-CuMgAl-LDH and C-CuMgAl-LDH samples

Fig. 2. The SEM (A and B) and TEM (C and D) of N-CuMgAl-LDH and C-CuMgAl-LDH

Fig. 3. The Cu2p_{3/2} XPS of N-CuMgAl-LDH and C-CuMgAl-LDH

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C_{sp}–H

Table 9 The catalytic results under different reaction conditions

Scheme 1 KIE experiment

Fig. 8. The Cu2p3/2 XPS of N-CuMgAl-LDH

Scheme 2 Proposed reaction pathway





Fig. 2. The SEM (A and B) and TEM (C and D) of N-CuMgAl-LDH and C-CuMgAl-LDH.

(A) and (C): N-CuMgAl-LDH, (B) and (D): C-CuMgAl-LDH.



Table 1 Sample notation and chemical compositions of the prepared samples.

Sample	Weight content (%)		Cu : Mg : Al	\mathbf{S}_{BET}	Pore volume	Average pore	nH ^a		
Sumple	Cu	Mg	Al	(mol)	(m^2/g) (cm^3/g) dia		diameter (nm)	pii	
N-CuMgAl -LDH	18.20	7.61	8.71	1:1.11:1.13	13.5	0.037	7.8	6.87	
C-CuMgAl -LDH	21.90	7.91	7.89	1:0.96:0.88	73.2	0.522	26.9	8.88	

^{*a*}Suspension of 0.3 g hydrotalcite in 20 mL deionized water.



Fig. 4. Plots of MS-NH₃-TPD signal versus temperature for the prepared LDHs.



Fig. 5. Py-IR spectra of the prepared C-CuMgAl-LDH and N-CuMgAl-LDH.

Catalyst	Amount of L acid site (µmol / g)	Amount of B acid site (µmol / g)	Total amount of L and B acid site (µmol / g)	B/L
N-CuMgAl -LDH	157.304	55.214	212.518	0.351
C-CuMgAl -LDH	114.752	10.296	125.049	0.090

Table 2 The amount of Lewis and Brønsted acid sites on different catalysts determined by Py-IR.

Table 3 Effect of the reaction solvent on the reaction.^a

+ CH ₃ N 1a 2a	+ CH_3NO_2 O_2 CuMgAI-LDH NO_2 2a 3aa					
	Entry	Solvent	Polarity	Conv. ^b /%	Sel. ^b /%	
	1	acetonitrile	6.2	34	79	
	2	1,4-dioxane	4.8	93	78	
	3	toluene	2.4	91	72	
	4	DMSO	7.2	93	74	
	5	methanol	6.6	40	48	
	6	proprylene glycol monomethyl ether	-	46	92	
	7	H ₂ O	10.2	95	56	

^{*a*}Reaction conditions: **1a** 0.5 mmol, **2a** 0.75 mmol, N-CuMgAl-LDH 0.2 g, 80 °C, reaction time 16 h, solvent 2 mL, oxygen atmosphere. ^{*b*}Based on the ¹H-NMR analysis (0.1 mmol 1,4-dinitrobenzene was used as the internal standard reference), and the by-products were not quantified.

Table 4 CDC reaction under different conditions.^a

Entry	Catalyst	2a/1a	Conv. ^b /%	Sel. ^b /%	TOF / h^{-1}
1	N-CuMgAl-LDH	1.5	93	78	-
2^c	N-CuMgAl-LDH	1.5	94	75	-
3	N-CuMgAl-LDH	3	94	84	-
4	N-CuMgAl-LDH	6	97	97	-
5^d	N-CuMgAl-LDH	6	>99	96	6.5
6^d	C-CuMgAl-LDH	6	78	92	4.8
7 ^{d, e}	N-CuMgAl-LDH	6	99	95	6.5
$8^{d, f}$	N-CuMgAl-LDH	6	97	96	6.5
$9^{d, g}$	N-CuMgAl-LDH	6	93	96	6.2

^{*a*}Reaction conditions: **1a** 0.5 mmol, N-CuMgAl-LDH 0.2 g, reaction time 16 h, 1,4-dioxane 2 mL, oxygen atmosphere. ^{*b*}Based on the ¹H-NMR analysis (0.1 mmol 1,4-dinitrobenzene was used as the internal standard reference), and the by-products were not quantified. ^{*c*}100 °C. ^{*d*}18 h. ^{*e*}First recycle. ^{*f*}Second recycle. ^{*g*}Third recycle.

 Table 5 Some representative heterogeneous catalytic systems for the CDC reactions between

 N-phenyl-1,2,3,4-tetrahydroisoquinoline and nitromethane.

•	Entry	Catalyst	Temp. /°C	Yield ^a /%	Time / h	Ref.
	1	N-CuMgAl-LDH	80	96 (85)	18	This work
	2	zero-valent nanoporous gold (AuNPore)	80	99 (95)	24	28
	3	$Fe_3O_4@SiO_2$ -bipy- AuCl_2] ⁺ [AuCl_4] ⁻ complex	60	(82)	8	29
	4	poly(2-methoxyaniline -5-sulfonic acid)/gold nanoparticles	50	91	18	64
	5	graphene-supported RuO ₂	60	(89)	24	30
	7	Fe ₃ O ₄ nanoparticles	100	(90)	24	65
	6	CuFe ₂ O ₄	100	(87)	24	38

^{*a*}The data in brackets were the isolated yield.



Fig. 6. Hot filtration test.

Reaction conditions: **1a** 0.5 mmol, **2a** 3.0 mmol, N-CuMgAl-LDH 0.2 g, 1,4-dioxane 2 mL, 80 °C, oxygen atmosphere.





3ma, 64 h, 71% **3na**, 17 h, 48%

^{*a*}Reaction conditions: **1** 0.5 mmol, **2a** 3.0 mmol, N-CuMgAl-LDH 0.2 g, 1,4-dioxane 2 mL, 80 ℃, oxygen atmosphere.

Table 7 CDC reactions between 2-phenyl-1,2,3,4-tetrahydroisoquinoline and nucleophiles with C_{sp3}-H.^a





^{*a*}Reaction conditions: **1a** 0.5 mmol, **2** 3.0 mmol, N-CuMgAl-LDH 0.2 g, 1,4-dioxane 2 mL, 80 °C,

oxygen atmosphere.

Table 8 CDC reactions between 2-phenyl-1,2,3,4-tetrahydroisoquinoline and nucleophiles with C_{sp2} -H or C_{sp} -H.^{*a*}





^aReaction conditions: 1a 0.5 mmol, 2 3.0 mmol, N-CuMgAl-LDH 0.2 g, 1,4-dioxane 2 mL, 80 °C, oxygen

atmosphere.

 Table 9 The catalytic results under different reaction conditions.

Entry	Catalyst	Additive	Conv. ^b /%	Sel. ^b %
1	N-CuMgAl-LDH	-	>99	96
2	-	-	76	45
3 ^c	N-CuMgAl-LDH	-	75	87
4^d	N-CuMgAl-LDH	-	70	89
5	Mg ₂ Al-LDH	-	24	62
6	CuMgAl hydroxide	-	48	56
7	CuCl ₂ ^e	-	>99	39
8	N-CuMgAl-LDH	BHT $^{\rm f}$	70	85
9	N-CuMgAl-LDH	CCl ₃ Br ^f	>99	54

^{*a*}Reaction conditions: **1a** 0.5 mmol, **2a** 6.0 equiv., catalyst 0.2 g, 80 °C, 18 h, 1,4-dioxane 2 mL, oxygen atmosphere. ^{*b*}Based on the ¹H-NMR analysis, and the by-products were not quantified. ^{*c*}Nitrogen atmosphere. ^{*d*}Air atmosphere. ^{*e*} CuCl₂ 0.03g. ^{*f*}1.5 equiv..



Scheme 1 KIE experiment.



Fig. 7. The Cu2p3/2 XPS of N-CuMgAl-LDH (A) before the reaction; (B) after the reaction under nitrogen;

(C) after the reaction under oxygen.



Scheme 2 Proposed reaction pathway.