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Synergistic catalysis of Cu⁺/Cu⁰ for efficient and selective N-methylation of nitroarenes with para-formaldehyde



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ABSTRACT

In this paper, an inexpensive heterogeneous copper nanoparticles catalyst derived from CuAl-layered double hydroxide via an *in situ* topotactic transformation process was developed. Cu nanoparticles with uniform size were homogeneously dispersed on amorphous Al_2O_3 with strong metal-support interaction. Characterization results reveals that the Cu^0 and Cu^+ were simultaneously formed with Cu^+ species as the dominant sites on the surface during the reduction process. The resultant catalyst Cu/Al_2O_3 demonstrates high catalytic activity, selectivity and durability for the reductive *N*-methylation of easily available nitroarenes in a cost-efficient, environmentally friendly and cascade manner. A broad spectrum of nitroarenes could be efficiently *N*-methylated to their corresponding *N*,*N*-dimethyl amines with good compatibility of various functional groups. The protocol is also applicable for the late-stage functionalization of biologically and pharmaceutically active nitro molecules. A structure-function relationship discloses that Cu^0 and Cu^+ sites on the surface pronouncedly boosts the reaction efficiency in a synergistic manner, in which Cu^0 could facilitate H_2 production and *N*-methylation of anilines, while Cu^+ is considerably more active and participates in the overall process of the selective *N*-methylation of nitroarenes. Moreover, the catalyst also showed a strong stability and could be easily separated for successive reuses without an appreciable loss in activity and selectivity.

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1. Introduction

N-methylation is one of the most fundamental transformation to form *N*-methylamines in organic chemistry, which represent important platform chemicals for bulk and fine chemicals as well as materials [1–3]. Besides, *N*-methylation, as a powerful synthetic method, allows for the late-stage functionalization by incorporating into a magic methyl group to regulate the biological and pharmaceutical properties of advanced life science molecules [4–6].

Traditional procedures for *N*-methylation typically employ the reactions of amines with powerful but carcinogenic methylating reagents [7–9], such as methyl iodide, dimethyl sulfate or diazomethane, which are operationally problematic and generally suffer from narrow scopes of amines and generation of a large amount of waste. In recent years, with the intensive awareness of environmental protection and the prevalence of "green chemistry", transition metal-catalyzed *N*-methylation of amines with more environmentally benign and safer methylating reagents, such as

* Corresponding author. E-mail address: yangyong@qibebt.ac.cn (Y. Yang). formic acid [10,11], (para)formaldehyde [12,13], methanol [14,15], CO₂ [16–18] and dimethyl carbonate [19,20] were employed. A number of homogeneous and heterogeneous metal catalysts have been developed for the transformation with considerable progress [21]. However, in these cases, harsh reaction conditions, such as high reaction temperature and pressure together with varying reductants, e.g., hydrosilanes, boranes, or molecular hydrogen are usually required to achieve satisfactory results accompanying with low atom efficiency and massive waste production, thereby significantly impeding their practical applications. Furthermore, aryl amines are most frequently used as starting materials for the synthesis of N-methylamines among these well-developed methods, which are generally prepared form reduction of readily available and inexpensive nitroarenes catalyzed by transition metals under high pressure of hydrogen. As such, from both economic and environmental perspectives, the development of a straightforward one-pot selective synthesis of N-methylamines from easily available nitroarenes with greener C1 source in a tandem and cost-effective manner is of great practical significance.

To date, only a handful of examples catalyzed by metal catalysts for one-pot direct *N*-methylation of nitroarenes to



N-methylamines using formic acid/ H_2 , (para)formaldehyde/ H_2 , methanol, CO_2/H_2 as C1 sources have been reported. In this regard, heterogeneous metal catalysts are mostly frequently employed owing to their advantages, such as catalyst recyclability and easy of separation from the reaction media (Scheme 1). In 2009, Li and co-workers reported the synthesis of N,N-dimethylanilines from nitroarenes with methanol catalyzed by a pretreated Raney-Ni catalyst under high temperature and N₂ pressure (170 °C, 3 MPa Ar) [22]. In 2013, Rong and co-workers developed a skeletal Cu (also as known as Raney-Cu) as chemoselective catalyst for onepot synthesis of N,N-dimethylanilinesfrom nitroarenes with formaldehyde in the presence of molecular hydrogen (1.5 MPa) [23]. Later on, Shi and co-workers developed two heterogeneous catalysts, e.g., CuAlO_x and Pd/CuZrO_x, for direct and selective N-methylation of nitro compounds with CO₂/H₂, respectively, while both required harsh conditions and longer reaction times (30–100 bar, 150–170 °C, 30–48 h) [24,25]. The same group subsequently reported TiO₂ supported nano-Pd catalyst (Pd/TiO₂) could enable the N-methylation of nitro compounds with methanol under UV irradiation at room temperature [26], and also allows for a kinetically controlled synthesis of N-monomethylamines from nitroarenes with formaldehyde in the presence of molecular hydrogen (1.0 MPa) [27]. Meanwhile, Cao and co-workers developed a Au/rutile catalyst for the synthesis of N,N-dimethlanilines from nitroarenes using formic acid (FA) as a benign C1 source, but high pressure of H₂ (4 MPa) and high temperature (140 °C) were required [28]. Remarkably, in 2017, Beller and co-workers made a great achievement and developed a non-noble iron oxide-based nanocatalyst (Fe₂O₃/NGr@C), which enables the efficient synthesis of a series of functionalized and structurally diverse *N*-methylamines from nitroarenes with *para*-formaldehyde as both methylating and reducing agent [29]. In this case, no necessity of any specialized equipment and use of additional reducing agents makes this protocol operationally simple and practical.

Apparently, there is a strong desire to develop a heterogeneous non-noble metal catalyst, which can enable efficient and selective *N*-methylation from inexpensive and readily available nitroarenes with green methylating agents in simple operation process under milder reaction conditions. Layered double hydroxides (LDHs) are a class of two-dimension (2D) anion-intercalated materials, which can be generally expressed by the formula $[M_{1-x}^{2+}M_x^{3+}(OH)] - (A^{n-})_{x/n} mH_2O. M^{2+}$ and M^{3+} metal cations are distributed at atomic level in the hydroxide layers, and Aⁿ⁻ is an anion located in the interlayer region [30,31]. Owing to their versatility in composition, morphology as well as unique structural topotactic transformation properties, LDHs have been extensively applied in photocatalysis [32-35], heterogeneous catalysis [36-41], and adsorption/separation processes [42-44]. As far as catalysis is concerned, the most attractive feature of LDHs is that the LDH precursors containing transition metal cations, e.g., Ni [45-47], Co [48-50], Fe [51], and Cu [52–54] can be *in situ* reduced to catalytically active metal nanoparticles supported to a mixed metal oxides with a high dispersion, strong metal-support interaction, and good stability in a morphologically control manner.

In this work, we developed a new heterogeneous catalyst with Cu nanoparticles supported on amorphous Al₂O₃ (denoted as Cu/ Al₂O₃) derived from CuAl-layered double hydroxide (LDH) precursor via an in situ topotactic transformation process. Cu nanoparticles were homogeneously and uniformly dispersed on amorphous Al₂O₃ with strong support-metal interaction compared with the catalyst *ip*-Cu/Al₂O₃ prepared using conventional impregnation method. The catalyst Cu/Al₂O₃ exhibited efficient and selective N-methylation of nitroarenes with para-formaldehyde in the absence of external molecular hydrogen under milder conditions. A broad set of nitroarenes including biologically relevant substrates were efficiently and selectively converted to their corresponding N,N-dimethyl amines in high to excellent yields with good tolerance of various functional groups. A combination study including comprehensive characterizations and control experiments discloses that: (1) the catalyst Cu/Al₂O₃ derived from CuAl-LDH results in a strong interaction between Cu nanoparticles and amorphous Al₂O₃ with formation of Cu⁺ and Cu⁰ active species with Cu⁺ as the major sites on the surface upon *in situ* topotactic transformation; (2) Cu⁰ and Cu⁺ sites synergistically boost the catalytic efficiency for the reductive N-methylation of nitroarenes, while Cu⁰ and Cu⁺ have their individual role in the entire process.

2. Experimental section

2.1. Preparation of catalysts

CuAl-layered double hydroxide (LDH) with the mole ratio of Cu: Al = 2:1 were synthesized by co-precipitation method. Typically, two aqueous solutions, a solution of the copper and aluminum nitrates (mole ratio of Cu:Al = 2:1) and a mixed solution of NaOH and Na₂CO₃ (mole ratio of NaOH:Na₂CO₃ = 5:1) precipitant, were simultaneously added dropwise to deionized water (100 mL) under vigorous stirring at room temperature. The pH during precipitation was kept at a constant value of 10 ± 0.2 . The precipitate was then aged at 60 °C for 16 h followed by filtering and washing thoroughly with deionized water. The filtration cakes were dried for 10 h at 50 °C in vacuum oven overnight. The obtained CuAl-LDH was reduced in a flow of 5% H_2/Ar (60 mL mim⁻¹) for 6 h at 300 °C, and the heating rate was 2 °C min⁻¹. The resulting catalyst was denoted as Cu/Al₂O₃. The catalyst *cal*-Cu/Al₂O₃ was prepared from firstly calcined of CuAl-LDH at air atmosphere at 500 °C for 6 h with 2 °C min⁻¹ in tube furnace (labelled as *cal*-CuO/Al₂O₃ catalyst), followed by a reduction in a flow of 5% H_2/Ar (60 mL mim⁻¹) for 6 h at 300 °C. Other layered double hydroxides, e.g., NiAl-LDH and CoAl-LDH were prepared following by the same method as described above. Their corresponding derived catalysts Ni/Al₂O₃ and Co/Al₂O₃ were also prepared similarly by in situ structural topotactic transformation process.

For comparison, the catalyst denoted as ip-Cu/Al₂O₃ as a control sample was prepared by a conventional impregnation method. The neutral Al₂O₃ (10.0 g) was dispersed into an aqueous solution of Cu (NO₃)₂·3H₂O (0.0157 mol L⁻¹, 10 mL). The suspension was stirred



Scheme 1. Illustration of discovery of heterogeneous catalysts for direct one-pot N-methylation from nitroarenes.

at 70 °C overnight, and the precipitate was then dried at 80 °C for 10 h. The obtained solid sample was calcined in air at 500 °C for 6 h (labelled as *ip*-CuO/Al₂O₃ catalyst) followed by H₂ reduction at 300 °C for 6 h.

2.2. Characterization methods

The X-ray diffraction (XRD) patterns of all the catalysts were obtained on a Bruker D8 Advance X-ray diffraction diffractometer equipped with Cu Ka radiation ($\lambda = 1.5147$ Å). The morphology of catalysts was examined by a H-7600 transmission electron microscopy (TEM), a Tecnai G2 F30 high-resolution TEM (HRTEM). Nitrogen adsorption-desorption data were obtained on a Micromeritics ASAP 2020 static volumetric sorption analyzer. The specific surface area of the samples was calculated by the Brunauer-Emmet-Teller (BET) method. Temperature programmed reduction (TPR) was performed in a quartz reactor with a thermal conductivity detector to record the consumption of H₂. The samples were reduced in a flow of 5 vol% H_2/Ar at a heating rate of 10 K min⁻¹ after pretreatment with Ar. The exposed copper surface area and the dispersion of Cu was determined by dissociative N₂O adsorption and operated on Micromeritics AutoChem 2920 instrument [55]. Irreversible CO adsorption isotherms were collected with a chemisorption module of the Micromeritics ASAP 2020 instrument [56-58]. Catalysts were firstly reduced in situ with 5 vol% H₂/Ar at 573 K for 4 h and then cooled to 300 K. A total adsorption isotherm was collected using 200-500 torr CO and the reversible adsorption isotherm was repeated at the same conditions after evacuating for 30 min. The difference between the total and reversible values was used to determine the irreversible isotherm. The X-ray photoelectron spectroscopy (XPS) data was collected on an ESCALAB 250Xi (Thermo Scientific, UK) instrument equipped with a monochromatized Al Ka line source. All the binding energies obtained were calibrated based on the C 1s peak at 284.8 eV. Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was conducted on a PerkinElmer Optima 5300 DV instrument.

2.3. One-pot direct N-methylation of nitroarenes

In a typical procedure, a sealable Schlenk reaction tube equipped with a magnetic stir bar was charged with the catalyst Cu/Al₂O₃ (6 mg, 27 mol% of Cu), *p*-nitrotoluene (0.25 mmol), *para*-formaldehyde (3.75 mmol), and Na₂CO₃ (0.5 mmol). Then, DMSO-water (3 mL, 1:1 v/v) was injected into the tube and the reaction was tested under stirring at 130 °C for 15 h. After completion of the reaction, the reaction mixture was extracted with ethyl acetate and then filtered. The liquid was analysed by GC and GC-MS on an Agilent HP-7890 instrument with a flame ionization detector (FID) and an HP-5MS capillary column (30 m, 0.25 mm i.d., 0.25 µm film thicknesses) using nitrogen as the carrier gas to determine the conversion and selectivity using mesitylene as an internal standard. The desired *N*,*N*-dimethylated amines were purified by column chromatography using an appropriate eluent and structurally confirmed by ¹H/¹³C NMR and HR-MS.

3. Results and discussion

3.1. Structure and morphology characterizations of Cu/Al_2O_3 derived from CuAl-LDH

The Cu nanoparticles (NPs) supported on Al_2O_3 (Cu/ Al_2O_3) was prepared on the basis of the *in situ* structural topotactic transformation of CuAl-layered double hydroxoide (CuAl-LDH) precursor according to the previously reported method [52–54]. The XRD pattern of CuAl-LDH precursor (Fig. 1a) shows diffraction peaks



Fig. 1. XRD pattern for (a) CuAl-LDH precursor, (b) Cu/Al_2O_3, (c) $\it cal-Cu/Al_2O_3,$ and (d) $\it ip-Cu/Al_2O_3.$

at $2\theta = \sim 12^{\circ}$, 24° , 32° , 36° , 40° , and 48° , respectively, which can be indexed to the (003), (006), (012), (009), (015) and (0012) planes, a characteristic feature of layered CuAl-LDH phase with CO_3^{2-} located in the interlayer region. A thin plate-shaped crystals morphology with a layer structure and good crystallization for the CuAl-LDH was confirmed by SEM image (Fig. 2A). Upon reduction or calcination process, the structure of CuAl-LDH was destroyed and decomposed to mixed metal and/or metal oxides. Consequently, the characteristic reflections of CuAl-LDH disappear, accompanied by the observation of five peaks centered at $\sim 35^\circ$, \sim 43°, \sim 51°, \sim 63° and \sim 74°, attributing to the characteristic reflections of metallic Cu (JCPDS# 04-0836, pink lines) and Cu₂O (JCPDS# 05-0667, blue lines) (Fig. 1b), respectively. However, no reflection of Al₂O₃ is observed, clearly indicating an amorphous phase. Meanwhile, the catalyst *cal*-Cu/Al₂O₃ prepared from the calcination of CuAl-LDH in air followed with H₂ reduction, also demonstrates similar diffraction peaks to that of Cu/Al₂O₃, but with a relatively stronger diffraction of metallic Cu (Fig. 1c). The average sizes of Cu NPs calculated by Cu (111) diffraction peak shows that d_{Cu} of Cu/Al₂O₃ with 20.0 nm is smaller than that of cal-Cu/Al₂O₃ (34.2 nm). As a reference sample, the catalyst *ip*-Cu/Al₂O₃ was prepared via a conventional impregnation method from dispersion of $Cu(NO_3)_2$ on Al_2O_3 followed by calcination and H_2 reduction, in which XRD pattern is different from that of Cu/Al₂O₃ or *cal*-Cu/ Al₂O₃. Apart from the appearance of Cu⁰ and Cu⁺ weak diffaraction peaks, the diffraction of a Al₂O₃ phase was clearly observed (Fig. 1d).

TEM measurements were performed to investigate the morphology and distribution of Cu species in the catalyst Cu/Al₂O₃. It was observed that Cu NPs with an average size of 22.5 nm are uniformly dispersed on amphorous Al₂O₃ with a high density (Fig. 2B). HR-TEM images (Fig. 2C and D) clearly show two crystalline phases disperse on Al₂O₃ with crystal lattice fingers of 0.209 and 0.246 nm corresponding to Cu (1 1 1) and Cu₂O (1 1 1) planes, respectively [59]. These observations are in good consistent with the XRD results and also reveal that Cu species were simultaneously present in the form of Cu^o and Cu⁺ on the surface of the catalyst Cu/Al₂O₃.

To further investigate the reducibility and the interaction between Cu phase and amorphous Al_2O_3 of over catalysts prepared by different methods, H_2 -TPR experiment was performed (Fig. 3). The TPR profile of *cal*-CuO/Al_2O₃ (Fig. 3a) exhibits a broad and strong hydrogen consumption peak ranging from 220 to 350 °C, accounting for the reduction of Cu²⁺ to Cu⁰ and Cu⁺, as evidenced by the coexistence of Cu⁰ and Cu⁺ in XRD and HR-TEM characterization. Cu⁺ species on the surface may result from the reduction of Cu²⁺ species having strong interaction with Al₂O₃, while Cu⁰ species are from the readily reduced CuO [55,60]. In contrast, the reduction behavior over *ip*-CuO/Al₂O₃ (Fig. 3b) had two hydrogen consumption peaks: the one starting from 180 °C to 280 °C is assigned to the reduction of Cu²⁺ species with weak interaction with Al₂O₃, and another broad peak at 300-450 °C is possibly due to the Cu species located into the channel of Al₂O₃ with of significant difficulty to be reduced [61]. Comparatively, the higher reduction temperature for the catalyst cal-CuO/Al₂O₃ strongly indicates the interaction between Cu NPs and Al₂O₃ is considerably enhanced via the in situ topotactic transformation from CuAl-LDH, which could make Cu NPs much harder for agglomeration during the preparation and reaction process as previous reports [45.62].

XPS analysis was performed to study the surface chemical state and distribution of Cu species in the catalysts. For the sample of



Fig. 2. (A) SEM image of CuAl-LDH, (B–D) HR-TEM images of the catalyst Cu/Al_2O_3 ; the inset shows the Cu nanoparticles size distribution.



Fig. 3. H₂-TPR profiles of (a) cal-CuO/Al₂O₃ and (b) ip-CuO/Al₂O₃.

CuAl-LDH, the Cu $2p_{3/2}$ peak at ~ 935.2 eV and Cu $2p_{1/2}$ peak at \sim 955.0 eV along with their satellite peaks are detected (Fig. 4A (a)), implying that Cu species in CuAl-LDH exist in the form of Cu(OH)₂. Upon in situ topotactic transformation under H₂ atmosphere (that is, Cu/Al₂O₃) or pretreatment with calcination in air followed by H₂ reduction (that is, *cal*-Cu/Al₂O₃), the reductive formation of Cu⁺ and Cu⁰ species occurs, as observed by the disappearance of the Cu 2p satellite peak at 941–944 eV together with a blue shift of binding energy (Fig. 4A (b and c)). Two overlapping peaks at 916.6 and 918.6 eV were observed in the Cu LMM Auger electron spectroscopies (XAES), further confirming the formation of Cu^+ (916.6 eV) and Cu^0 (918.6 eV) (Fig. 4B) on the catalyst surface. These observations are in well consistent with the results of XRD and HR-TEM. Furthermore, deconvoluation analysis of two XAES peaks discloses that the composition ratio of Cu^+/Cu^0 in the catalysts Cu/Al₂O₃ and cal-Cu/Al₂O₃ is 2.8 and 1.6, respectively. To further quantitatively measure Cu⁺ species on the surface of these two catalysts, irreversible CO adsorption experiments were executed. It is well-established that Cu⁺ species can irreversibly bind with CO molecule, while CO is easily desorbed from Cu⁰ and Cu²⁺ sites [56]. As shown in Fig. 5, the catalyst Cu/Al₂O₃ exhibited a significantly larger value of CO uptake than that of *cal*-Cu/Al₂O₃ (76.1 vs 24.8 μ mol/g), evidencing the exposure of a much higher content of Cu⁺ species on Cu/Al₂O₃ surface.





Fig. 4. (A) Cu 2p XPS spectra for (a) CuAl-LDH, (b) Cu/Al₂O₃, and (c) cal-Cu/Al₂O₃ and (B) Cu LMM Auger electron spectra for Cu/Al₂O₃, and (c) cal-Cu/Al₂O₃.



Fig. 5. Irreversible CO adsorption isotherms for (A) Cu/Al₂O₃ and (B) cal-Cu/Al₂O₃.

3.2. Selective N-methylation of nitroarenes with para-formaldehyde

We initiated our attempts for the one-pot selective *N*-methylation of *p*-nitrotoluene with *para*-formaldehyde as a benchmark reaction to investigate the catalytic performance of the catalyst Cu/Al₂O₃. A rapid screening of various parameters including solvents, bases, amounts of *para*-formaldehyde and reaction times shows that the maximum outcomes could be obtained using the following optimal conditions (6 mg of Cu/Al₂O₃, 15 equivalent of *para*-formaldehyde with respect to **1a**, 2 equivalent of Na₂CO₃ as a base, DMSO/H₂O (1:1, v/v) at 130 °C) (see Table S2, ESI). Under the optimized conditions, full conversion of **1a** with exclusive selectivity to *N*,*N*-dimethyl amine **2a** was achieved after 15 h (Table 1, entry 1). In the absence of either a catalyst, or *para*-formaldehyde, or a base, no reaction took place at all, indicating a combination of all of them is prerequisite for the success of the reaction (Table 1, entries 2–4).

For comparison, the catalysts *cal*-Cu/Al₂O₃ and *ip*-Cu/Al₂O₃ with co-existence of Cu⁺ and Cu⁰ species on the surface were catalytically active for the reaction, while 46.3 and 26.4% conversion of **1a** were merely achieved, respectively, albeit with perfect selectivity to **2a** under identical conditions (entries 6 and 7). In sharp contrast, CuAl-LDH was also employed as the catalyst for the reaction but failed to give any product under otherwise identical conditions (entry 5), suggesting that Cu²⁺ species are not active for the reaction. In addition, other layered double hydroxide precursors, such as NiAl-LDH, CoAl-LDH, and even their derived corresponding catalysts upon a H₂ reduction process, all demonstrated inert feature for *N*-methylation of **1a** with no reactivity (entries 8–11), clearly indicating that the key role of Cu/Al₂O₃ in catalysis.

Such a significant difference in catalytic performance, especially between Cu/Al₂O₃ and *cal*-Cu/Al₂O₃, inspires us to further distinguish the individual role of Cu⁰ and Cu⁺ sites for *N*-methylation. To this end, firstly, the metallic Cu powder and Cu₂O were subjected to *N*-methylation of **1a** under the optimized conditions. It was found that Cu₂O gave substantial reactivity with 38% conversion of **1a** toward **2a**, while Cu powder showed no reactivity at all (Fig. 6). Such results strongly imply that Cu⁺ sites are primarily responsible for the reductive *N*-methylation of nitroarene. However, Cu⁰ as a possible active sites involving in this cascade process can't be ruled out. Next, a set of control experiments were further performed to elucidate the individual role of Cu⁰ and Cu⁺.

We firstly performed the products distribution as a function of reaction time using the benchamrk reaction under the optimized conditions to disclose the possible reaction pathway. As shown in Fig. 7, at the early stage of the reaction (within 1 h), p-nitrotoluene (1a) was rapidly consumed and converted into mixture of products, including *p*-methylaniline (**4a**), a *N*-*p*-tolylmethanimine (**3a**), *N*-monomethyl-*p*-toluidine (**5a**), and *N*,*N*-dimethyl-*p*-toluidine (**2a**). With an elapse of the reaction times, the formation of the desired 2a started to dominate the reaction till complete formation of 2a, whereas 3a, 4a and 5a were simultaneously and gradually consumed. As such, the reaction profiles clearly demonstrate the N-methylation of nitroarenes with paraformaldehyde proceeded in an one-pot, direct and stepwise pathway. More specifically, the reaction pathway most likely involves a release of molecular hydrogen from para-formaldehyde for selective reduction of nitroarene and the corresponding imine after condensation with formaldehyde to afford the mono-N-methylated amine. A subsequent second condensation with formaldehyde followed by reduction again finally yields the *N*,*N*-dimethylamine. Obviously, the *in situ* generation of H₂ for reduction of nitroarene towards aniline and its subsequent N-methylation with formaldehyde are two key reaction steps in the entire process.

After awareness of the reaction pathway, we next investigated the two key reaction steps in detailed. The release of H_2 from *para*formaldehyde over various catalysts was carried out under the optimized conditions, and the results are compiled in Table S3. Either Cu⁰ or Cu⁺ species could facilitate the generation of molecule hydrogen from *para*-formaldehyde in the presence of H₂O [63]. In each case, H₂ and CO₂ were detected as confirmed by GC-TCD analysis (Fig. S2). Cu₂O gave higher H₂ release capacity than Cu powder

Table 1

Catalyst screening in one-pot N-methylation of p-nitrotoluene ^a.



Entry	Catalyst	$(CH_2O)_n$ (eq.)	Base	Conversion (%) ^b	Selectivity (%) ^b
1	Cu/Al ₂ O ₃	15	Na ₂ CO ₃	100	100
2	_	15	Na ₂ CO ₃	-	-
3	Cu/Al_2O_3	15	_	-	-
4	Cu/Al_2O_3	-	Na ₂ CO ₃	-	-
5	CuAl-LDH	15	Na ₂ CO ₃	-	-
6	cal-Cu/Al ₂ O ₃	15	Na ₂ CO ₃	46.3	100
7 ^c	ip-Cu/Al ₂ O ₃	15	Na ₂ CO ₃	26.4	100
8	NiAl-LDH	15	Na ₂ CO ₃	-	-
9	CoAl-LDH	15	Na ₂ CO ₃	-	-
10	Ni/Al ₂ O ₃	15	Na ₂ CO ₃	-	-
11	Co/Al ₂ O ₃	15	Na ₂ CO ₃	-	-

^a Reaction conditions: *p*-nitrotoluene, (0.25 mmol); catalyst, (6 mg); (CH₂O)_n (15 eq.); Na₂CO₃ (2 eq.); H₂O/DMSO = 1:1, (3 mL).

^b Conversion and selectivity were obtained by GC using mesitylene as an internal standard.

^c The catalyst dosage was 40 mg (27 mol% Cu).



Fig. 6. Synergistic role of Cu^0/Cu^* for the benchmark reaction under the optimized conditions. Reaction conditions: *p*-nitrotoluene, (0.25 mmol); Cu powder (10 mg) or Cu₂O (10 mg); (CH₂O)_n (15 eq.); Na₂CO₃ (2 eq.); H₂O/DMSO = 1:1, (3 mL).

did (0.237 vs 0.107 mL/mg), clearly indicating that Cu⁺ sites are preferential and more active for in situ generation of molecular hydrogen from para-formaldehyde. Similarly, Cu/Al₂O₃ generated relatively larger amount than that of cal-Cu/Al₂O₃ (0.775 vs 0.57 mL/mg) under identical conditions, due to the a larger Cu⁺ content on the surface, further confirming the more active feature of Cu⁺ for H₂ generation. Subsequently, we investigated the reactivity of Cu powder and Cu₂O for N-methylation of p-methylaniline (4a) with para-formaldehyde under the standard conditions. The results revealed that either Cu⁰ or Cu⁺ sites are effective for the direct N-methylation of anilines, whereas Cu⁺ sites are more reactive than that of Cu⁰ to a certain extent, along with the formation of a mixture of mono- and di-methyl amines with the desired **2a** being the major product (Scheme 2, Eqs. (4) and (5). Likewise, the catalyst Cu/Al_2O_3 also outperformed the N-methylation of p-methylaniline with para-formaldehyde in comparison with cal-Cu/Al₂O₃ under the standard conditions



Fig. 7. The products distribution as a function of reaction times for the benchmark reaction over Cu/Al₂O₃ under the optimized conditions.

(Scheme 2, Eqs. (1) and (2), mainly accounting for its larger content of Cu^+ sites on the surface. Besides, the catalyst Cu/Al_2O_3 could efficiently convert **5a** to **2a** under identical conditions (Scheme 2, Eq. (3)).

Given the inert feature of Cu^0 for the *N*-methylation of **1a** with *para*-formaldehyde, the benchmark reaction in the presence of a mixture of Cu powder and Cu₂O was performed under otherwise identical conditions. Surprisingly, a pronounced enhancement in activity was observed compared with the reaction in the only presence of Cu₂O (Fig. 6). Therefore, taken all control experimental results together, a synergistic role of Cu⁰ and Cu⁺ responsible for this direct and efficient reductive *N*-methylation of nitroarenes with *para*-formaldehyde is proposed. In the entire process, Cu⁰ could facilitate both the generation of H₂ and *N*-methylation of anilines, while Cu⁺ is highly active for participating in each individual reaction as shown in Scheme 3.

After identifying the optimized conditions and the plausible reaction pathway, we next investigated the general applicability of this reductive *N*-methylation protocol. Generally, the catalyst Cu/Al₂O₃ proceeded the *N*-methylation reaction efficiently for various nitroarenes bearing with electron-donating or electron-withdrawing substituents on the phenyl ring, affording their respective *N*,*N*-dimethyl amines in decent to high yields, as shown in Table 2. The nitroarenes incorporating with electron-donating groups, such as -CH₃, -OH, -OCH₃, -NH₂ groups, could give corresponding *N*,*N*-dimethyl amines in excellent yield (**2b-2h**). However, the nitroarenes substituted with electron-withdrawing groups dramatically decreased the efficiency (**2o-2q**), indicating



Scheme 3. Reaction pathway for stepwise reductive *N*-methylation of nitroarenes with *para*-formaldehyde over Cu/Al₂O₃.

that *N*-methylation reaction of nitroarenes is a typical nucleophilic feature. Apparently, the substituents in the *para*, *meta*, and *ortho* of phenyl ring are compatible with reaction conditions. The substrates with *ortho* position appeared to be less reactive than their *para* or *meta* substituted analogues, indicating the *ortho*-substituted groups have a negative influence on the reaction



Scheme 2. Control experiments.

Table 2Substrate scope of functionalized nitroarenes a.



 a Reaction conditions: nitroarenes (0.5 mmol), Cu/Al_2O_3 (12 mg, 27 mol% Cu), (CH_2O)_n (15 eq.), H_2O/DMSO (6 mL, 1:1 v/v), 130 °C. Yields of isolated products are given.

efficiency, most likey due to the steric effect. Importantly, halogensubstituted nitroarenes were converted to corresponding *N*,*N*-dimethyl amines without observation of dehalogenation (**2i-2n**), which can be used for further functionalization via a coupling reaction. Gratifyingly, nitroarenes bearing readily reducible functional groups, such as nitrile (**10**), aldehyde (**1p**) and ester (**1q**), were successfully dimethylated and the reducible groups remained untouched, highlighting the excellent chemoselectivity of the catalyst Cu/Al₂O₃ under the present conditions. In addition, nitroarenes containing heteroatom were also applicable to this protocol. For example, 3-nitropyridine and 6-nitroquinoline were smoothly dimethylated to give their respective **2r** and **2s** in 81 and 72% yields, respectively.

To demonstrate the potential application of this methodology, we performed the reductive *N*-methylation of several biologically active nitro-substituted molecules (Scheme 4). To our delight, fluorenone, nimisulide, and nimodipine were successfully incorporated with dimethyl groups in good yields without affecting other functionalities or the core-structure of the molecules, further implying the practical utility of this protocol.

The catalyst Cu/Al₂O₃ also showed good stability. After ten successive reuses, the conversion of *p*-nitrotoluene (**1a**) presented a slight decrease, while the selectivity to *N*,*N*-dimethyl*p*-toluidine (**2a**) maintained a high value for the benchmark reaction under the optimized conditions (Fig. 8). The decrease of catalytic activity mainly accounts for the mass loss of the catalyst in each cycle and the growth of Cu/Cu₂O particles in the catalyst upon recycle as evidenced by XRD characterization (Fig. S3).



Scheme 4. Synthesis of pharmaceutical N, N-dimethylamines from the corresponding nitro molecules.



Fig. 8. Catalyst recycling and reusability of Cu/Al_2O_3 for the benchmark reaction under the optimized conditions.

4. Conclusions

In conclusion, we have developed a low-cost copper nanoparticles catalyst derived from two-dimension CuAl-layered double hydroxide via a facile and *in situ* topotactic transformation process. The resultant catalyst Cu/Al₂O₃ demonstrated remarkable efficiency for one-pot reductive *N*-methylation of easily available nitroarenes with *para*-formaldehyde with good compatibility of various functional groups under mild conditions. The coexistence of Cu⁰ and Cu⁺ on the surface are synergistically responsible for the efficient reaction. This direct synthetic methodology using inexpensive Cu-based catalyst under facile conditions is a promising process that has the potential to enable selective *N*-methylation especially late-stage functionalization of biologically relevant nitro compounds from practical point of view.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2019.06.022.

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