Field-induced concentration and low coordination-enhanced adsorption boost electroreductive deuteration of nitriles over copper nanotips

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Abstract

Electrochemical deuteration utilizing D$_2$O is a promising room-temperature strategy for synthesizing deuterated molecules. At present, high Faradic efficiencies (FEs) at high reaction rates are extraordinarily significant but highly challenged. Here, high-curvature low-coordinated copper nanotips (LC-Cu NTs) are designed to enable electroreductive deuteration of $\alpha$-deuterio aryl acetonitriles, in situ generated from fast $\alpha$-H/D exchange of acetonitriles in D$_2$O, to $\alpha,\beta$-deuterio arylethyl primary amines with 90% FE and 0.11 mmol h$^{-1}$ cm$^{-2}$, greatly outperforming the reported data and other Cu counterparts. The increased electric fields of the nanotips concentrate nitriles and K$^+(D_2O)_n$, and low-coordination sites promote nitriles and D$_2$O adsorption, thus facilitating nitrile deuteration with an excellent reaction rate. The higher coupling energy barrier of active hydrogen atoms at low-coordination sites restricts the D$_2$ evolution, accounting for the outstanding FE. The wide substrate scope, easy gram-scale synthesis, and facile preparation of $d_4$-melatonin with enhanced antitumor and antioxidation effects highlight its great promise. Furthermore, the application of LC-Cu NTs in other deuteration reactions with improved reaction rates and FEs rationalizes the design concept.

Full Text

The presence of deuterium (D) can alert the pharmacokinetic profiles, reduce the dose, and lower the lethality of drugs due to the more stable C-D bond than the C-H bond.$^{1-6}$ In 2017, the US Food and Drug Administration approved the first deuterated drug, deutetramelatonin (Austedo™), for an enhanced treatment of the Huntington's disease compared with its unlabeled version of tetrabenazine (Fig. 1a).$^7$ Later, substantial effort was devoted to synthesizing and patenting deuterated pharmaceuticals.$^{8-12}$ Arylethyl amine subunits prevail in a variety of pharmaceuticals that display distinct biological activities toward human diseases (Supplementary Fig. 1),$^{13,14}$ showing the structural significance of such skeletons in drug design and discovery. It is reasonable to anticipate that introduction of D at the arylethyl amine moieties will further improve the pharmaceutical properties of the drug. Many deuterated drug molecules with D at the $\alpha$- and $\beta$-positions adjacent to N atoms have demonstrated enhanced metabolic stability and bioactivity, and some have been submitted to clinical trials (Fig. 1a).$^{3,15,16}$ Furthermore, arylethyl primary amines (AEPAs) constitute essential and versatile building blocks for fabricating drugs containing arylethyl amine frameworks.$^{7,13,14,17,18}$ Therefore, searching for an efficient method for the synthesis of $\alpha,\beta$-deuterio arylethyl primary amines ($\alpha,\beta$-DAEPAs) with a high deuterated ratio will promote the development of deuterated drugs.

Typically, two-pot reaction systems are adopted to synthesize $\alpha,\beta$-DAEPAs, which consist of the formation of $\alpha$-deuterio aryl acetonitriles ($\alpha$-DAANs) from the H/D exchange of aryl acetonitrile (AANs) followed by reductive deuteration of nitrile (C≡N) group in different reactors (Fig. 1b).$^{19,20}$ The requirement of such two-pot procedures may be due to the difficult compatibility of reaction conditions for the formation and subsequent deuteration of $\alpha$-DAANs for one-pot synthesis. Despite their dominance, expensive deuterated...
sources (e.g., NaBD$_4$, LiAlD$_4$, D$_2$) and strictly controlled anhydrous conditions are often required. The purification of $\alpha$-DAANs is always manpower- and time-consuming. These intrinsic factors bring about operating complexities, safety risks, and environmental issues, restricting their practical applications. In sharp contrast, a one-pot reaction system for the synthesis of $\alpha$$\beta$-DAEPAs by employing AANs and readily available deuterated sources is highly promising and desirable. A tandem H/D exchange-reductive deuteration strategy was developed for the one-pot synthesis of $\alpha$$\beta$-DAEPAs from AANs and D$_2$O under an inert atmosphere.$^{21}$ However, the reduction reagent samarium(II) iodide was strictly required only when the H/D exchange reaction was complete in 16 h before the subsequent reduction of C≡N. Additionally, the deuterated ratios of some products were between 14% and 31%. Therefore, developing a more facile one-pot reaction course to integrate a fast H/D exchange of AANs to $\alpha$-DAANs in tandem with reductive deuteration of $\alpha$-DAANs in D$_2$O for efficient synthesis of $\alpha$$\beta$-DAEPAs with high deuterated ratios is extremely significant but remains a challenging task.

Renewable electricity-powered transformation is becoming a powerful tool in synthetic chemistry.$^{22-27}$ Electrocatalytic deuteration via D$_2$O electrolysis has aroused increasing interest because D$_2$O can be easily activated under electrochemical conditions, providing an efficient and reliable way to synthesize deuterated molecules.$^{28,29}$ For example, the Cheng group demonstrated an electrochemical reductive deuteration of unsaturated C=C and C≡C bonds by using D$_2$O over a graphite felt (GF) cathode.$^{30}$ However, the C≡N bond in the substrate was retained well, implying the powerlessness of GF on the deuteration of nitriles. Recently, our group reported a low-coordination iron-promoted electroreductive deuteration of C≡N combined with K$_2$CO$_3$-assisted quick $\alpha$H/D exchange of AANs with D$_2$O for the one-pot synthesis of $\alpha$$\beta$-DAEPAs.$^{31}$ However, the Faradic efficiency (FE) of $\alpha$$\beta$-DAEPAs was only 20% owing to the competitive deuterium evolution reaction (DER). Additionally, gram-scale synthesis of $\alpha$$\beta$-DAEPAs was unsuccessful, which was due to the long reaction time causing enhanced hydrolysis side reaction of C≡N under basic conditions.$^{32}$ The slow reaction rate and low FE are two main obstacles impeding the practical applications of current electrochemical deuteration strategies using D$_2$O. Therefore, designing a catalytic material that shows good universality to many reactions to accelerate the reaction rate and inhibit the competitive DER is highly desirable. This will be conducive to achieving a scale-up electrosynthesis of deuterated compounds with improved D$_2$O utilization.

Herein, our theoretical predictions reveal that the high curvature nanostructures with increasing local electric fields along the tips can concentrate electrolyte cations (K$^+$), which will lead to a high local concentration (Con.) of water molecules. The low-coordination sites of copper (Cu) can enhance the adsorption of nitriles and water, promote H$_2$O electrolysis, and inhibit the hydrogen evolution reaction (HER). These factors speed up the electroreductive deuteration of nitriles with an enhanced FE. Thus, high-curvature low-coordinated Cu nanotips (LC-Cu NTs) are prepared via the in situ electroreduction of copper oxide (CuO) NTs. The LC-Cu NTs demonstrate excellent activity toward electrocatalytic reductive deuteration of $\alpha$-DAANs in situ generated from fast $\alpha$H/D exchange of AANs with D$_2$O for the synthesis of $\alpha$$\beta$-DAEPAs up to 97% selectivity, 99% deuterated ratio of both $\alpha$- and $\beta$-D, 90% FE, and a reaction rate
of 0.11 mmol h\(^{-1}\) cm\(^{-2}\) (Fig. 1c), greatly superior to the Cu NTs obtained by thermal reduction with hydrogen (Cu-H\(_2\) NTs), LC-Cu nanorods (NRs), and LC-Cu nanosheets (NSs). This one-pot deuteration strategy can tolerate a variety of different types of nitriles and enable gram-scale synthesis of \(\alpha,\beta\)-DAEPAs for deuterated drugs. Furthermore, the reaction rates and FEs of other electrocatalytic deuteration reactions can also be significantly improved over the LC-Cu NTs cathode.

Designing a low-coordination Cu nanotip cathode

Because the base-assisted H/D exchange of AANs with D\(_2\)O is irrelevant to electrocatalysis\(^{19,20,31}\), the rate and FE of the whole reaction are highly dependent on the C≡N reductive deuteration step. Cu-based materials are widely studied as electrode candidates in electrocatalytic CO\(_2\) and acetylene hydrogenation reactions\(^{33-35}\). Recently, the Lv group has made great progress in realizing the electrocatalytic hydrogenation of aliphatic nitriles over Cu nanosheets (NSs) cathode\(^{36}\). However, the Cu NSs are not efficient for the one-pot synthesis of \(\alpha,\beta\)-DAEPAs from AANs and D\(_2\)O (Supplementary Fig. 2). We hypothesize that this may be ascribed to the poor activation of AANs and D\(_2\)O by Cu NSs. Thus, we carried out density functional theory (DFT) calculations to provide preliminary theoretical guidance for the design of a more effective Cu catalyst to enhance the reaction rate and FE of the electroreduction of C≡N (Fig. 2a and Supplementary Note. 1). Acetonitrile (AN) and H\(_2\)O were used to replace aryl acetonitriles and D\(_2\)O to simplify the simulation process. It has been known that catalysts with a high curvature will generate a large local electric field on their tips, which can concentrate the reactants, thus accelerating the reaction\(^{37-39}\). As shown in Fig. 2b, the electric field intensity along the tips is greatly enhanced when the cone is sharpened from 50 nm (left) to 5 nm (right). This is attributed to electrostatic repulsion that causes free electrons to migrate to the tips of the Cu electrode\(^{37}\). The Gouy-Chapman-Stern model is used to estimate the effect of locally enhanced electric fields on Con. of adsorbed electrolyte cations K\(^+\). The mapped surface-adsorbed K\(^+\) Con. in the Helmholtz layer adjacent to the Cu electrode surface increases gradually with decreasing curvature radius (Fig. 2c). Therefore, the Con. of H\(_2\)O (in the form of K\(^+(\text{H}_2\text{O})_n\), where \(n\) refers to the number of H\(_2\)O molecules) around the tips will be increased by the concentrated K\(^+\). Additionally, it has also been reported that the tip structure can concentrate reactants\(^{39}\). Thus, the enriched local concentration of substrates and H\(_2\)O will be favorable to promote the electroreduction process.

Commonly, the hydrogenation of nitriles to primary amines proceeds via a two-step procedure involving an imine intermediate (C≡N→CH=NH→CH\(_2\)NH\(_2\))\(^{26,31,36,40}\). Enhancing the adsorption of substrates and H\(_2\)O on the electrode surface is usually favorable to accelerate their activation and the formation of active hydrogen (H\(^*\)) from water electrolysis, thus boosting the electrocatalytic hydrogenation reactions. In addition, introducing low-coordination sites into electrode materials is an efficient way to greatly increase the intrinsic activity of active sites by optimizing the local electronic properties\(^{31,41-42}\). As Fig. 2d shows, the \(d\) band center of LC-Cu upshifts toward the Fermi level compared with coordination-saturated Cu (CS-Cu), which is conducive to enhancing the adsorption of AN and the related imine intermediate,
thus observing greater adsorption energy ($E_{ads}$) of AN and imine on LC-Cu than those on CS-Cu (Fig. 2e). However, the $E_{ads}$ of the amine product is smaller on LC-Cu than on CS-Cu (Fig. 2f and Supplementary Fig. 3), which is helpful for product desorption to regenerate the catalytic sites. This may be due to the different adsorption modes or distinct electron-withdrawing and electron-donating properties of $\text{C}≡\text{N}$ and $\text{CH}_2\text{NH}_2$ groups on Cu sites. Furthermore, Fig. 2g reveals that the presence of low-coordination sites can increase the adsorption and lower the dissociation energy of $\text{H}_2\text{O}$ (1.34 vs. 1.73 eV), thus promoting $\text{H}_2\text{O}$ electrolysis to form $\text{H}^*$. These factors combined with the increased concentration of nitriles and $\text{H}_2\text{O}$ induced by the tip structures will together accelerate the electrocatalytic hydrogenation of nitriles. Last, the larger binding energy of $\text{H}^*$ over LC-Cu (1.45 vs. 1.05 eV) restricts the evolution of $\text{H}_2$ (Fig. 2g and Supplementary Figs. 4 and 5), improving the FE of the hydrogenation of nitriles. These theoretical predictions encourage us to synthesize a high-curvature low-coordinated Cu nanotip cathode for implementing the electroreductive deuteration of nitriles using D$_2$O with a high reaction rate and FE.

**Synthesis and characterization of the LC-Cu NTs.**

Self-supported LC-Cu NTs with abundant active sites on Cu foam are synthesized by electrochemical reduction of CuO NTs in 0.5 M $\text{K}_2\text{CO}_3$ electrolyte at -1.0 V vs. Hg/HgO (all the potentials in this work refer to Hg/HgO unless otherwise stated) (Fig. 3a). The disappearance of the cathodic peak belonging to CuO from the LSV curves reveals the full conversion of CuO to Cu(0) (Supplementary Fig. 6). Due to oxygen stripping from the precursor under mild electrochemical conditions, a large number of low-coordination sites are formed on metallic Cu.$^{41,42}$ The scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images reveal that the morphology of Cu nanotips is maintained well after the electroreduction of CuO NTs (Fig. 3b and Supplementary Fig. 7). In situ Raman spectroscopy (Fig. 3c) shows that the peak located at 292.5 cm$^{-1}$ belonging to CuO disappears with electrochemical reduction, and the peaks of Cu$_2$O (147.3 and 216.4 cm$^{-1}$) gradually arise and then disappear, proving the electroreduction-induced conversion process of CuO $\rightarrow$ Cu$_2$O $\rightarrow$ Cu.$^{43,44}$ Furthermore, the X-ray diffraction (XRD) pattern indicates that all the peaks can be indexed to Cu (JCPDS No. 04-0836).$^{43,44}$ (Fig. 3d). The peaks in the X-ray photoelectron spectroscopy (XPS) spectra located at 951.5 eV and 931.8 eV belong to Cu$^0$ 2$p_{1/2}$ and Cu$^0$ 2$p_{3/2}$, respectively (Fig. 3e). As a comparison, the Cu-H$_2$ NTs are synthesized by the thermal reduction of CuO NTs in 3% H$_2$/Ar at 350 °C for 2 h. The SEM and TEM images and XRD pattern demonstrate their successful preparation (Supplementary Fig. 8).

Moreover, to gain the electronic structure and coordination environment of LC-Cu NTs, X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS) are examined. The absorption-edge position of LC-Cu is located between that of CuO NTs and Cu foil (Fig. 3f), indicating a higher valence state for LC-Cu NTs owing to the presence of low-coordination sites. The EXAFS spectra are subjected to the continuous Cauchy Wavelet Transform (WT), and the similar spectra of LC-Cu NTs and Cu foil further indicate the complete transformation of CuO to Cu (Fig. 3g). The Fourier transformed $k^3$-weighted Cu-K edge EXAFS spectra show the new appearance of the Cu–Cu path in the reduced
sample (approximately 2.23 Å), while the average Cu−Cu coordination shell of LC-Cu NTs is lower than that of Cu foil and Cu-H\textsubscript{2} NTs (Fig. 3h). The Fourier transform of the Cu K-edge in the R space plot is fitted with the least-squares method to precisely determine the average coordination number. The fitting results (Supplementary Fig. 9 and Supplementary Table 1) show that the Cu−Cu coordination number of LC-Cu NTs is 7.3, which is much smaller than that of Cu foil (12). These results indicate that LC-Cu NTs formed via electroreduction of CuO NTs possess more low-coordination sites, which can be expected to facilitate electroreductive deuteration of nitriles in D\textsubscript{2}O with a high FE.

**One-pot synthesis of \(\alpha,\beta\)-DAEPAs via H/D exchange followed by electroreductive deuteration of nitriles over the LC-Cu NTs cathode in D\textsubscript{2}O.**

The \(\alpha\)-H/D exchange of 0.1 mmol of \(p\)-methoxyphenylacetonitrile (\(1a\)) can be finished within 2 min in a mixed solution of 1,4-dioxane (Diox)/0.5 M D\textsubscript{2}O solution of K\textsubscript{2}CO\textsubscript{3} (To simplify, Diox/0.5 M K\textsubscript{2}CO\textsubscript{3} is used thereafter) (Supplementary Fig. 10), which is faster than the reductive deuteration of C≡N, ensuring a high deuterated ratio of \(\alpha\)-D. Commonly, the one-pot deuteration reaction is carried out in a divided three-electrode reactor by using 0.1 mmol of \(1a\) as the model substrate in a mixed solution of Diox/0.5 M K\textsubscript{2}CO\textsubscript{3} (1:6 v/v, 7 mL) under constant potentials. The cycle-dependent cyclic voltammogram (CV) curve (red line) over the LC-Cu NTs cathode reveals an obvious reduction peak centred at approximately -0.78 V after adding \(1a\) into the cathodic cell (Fig. 4a), which is more positive than the reduction potential of D\textsubscript{2}O at approximately -0.98 V (blue line). This implies the easier electroreduction of \(1a\) than D\textsubscript{2}O. Potential-screened experiments show that the optimal results, including 94% conversion (Conv.) of \(1a\) (94%) and 97% selectivity (Sele.) with 90% FE of the deuterated amine product \(2a\) can be obtained at -1.3 V under the theoretical 38.6 coulombs (C) of electricity (Fig. 4b, Supplementary Fig. 11, and Supplementary Note 2). The decreased Conv. and FE at more negative potentials are attributed to the increased D\textsubscript{2} evolution reaction. In contrast, the Cu-H\textsubscript{2} NTs display much worse performance of Conv. and FE at the same potentials compared with those of LC-Cu NTs (Fig. 4c). A more negative potential of -1.4 V is required to achieve the best outcome (79.5% Conv. and 66.6% FE) over the Cu-H\textsubscript{2} NTs. These results further demonstrate the promoting effect of more low-coordination sites on the transformation of \(1a\) and FE of \(2a\). Time-dependent transformations show that 90% Conv. of \(1a\) can be obtained in 0.6 h, and the reaction rate is 0.11 mmol h\(^{-1}\) cm\(^{-2}\) at full Conv. of \(1a\) (Fig. 4d), 5.8 times faster than the reaction rate (0.019 mmol h\(^{-1}\) cm\(^{-2}\)) of our previous work.\(^{31}\) Additionally, a 67 h continuous electrolysis of \(2a\) over LC-Cu NTs is realized by using a flow reactor at -1.3 V (Fig. 4e and Supplementary Note 3). No obvious alteration of the current density and only an 8% decline of the FE are observed. SEM, TEM, and XRD characterizations (Supplementary Fig. 12) display no clear changes in the used sample, demonstrating the robust durability of LC-Cu NTs.

**Mechanistic study of the electroreductive deuteration of aryl acetonitriles.**

Because the \(\alpha\)-H/D exchange of AANs with D\textsubscript{2}O occurs through a fast and catalysis-irrelevant process, mechanistic studies are focused on the electroreductive deuteration of nitriles. Several experiments and
theoretical calculations are conducted to explore the reaction mechanism of electroreductive deuteration of nitriles over the LC-Cu cathode. First, to demonstrate the field-induced concentration roles of LC-Cu NTs to nitriles and K⁺, LC-Cu NRs and LC-Cu NSs were synthesized according to a similar procedure with LC-Cu NTs (Supplementary Fig. 13 and Supplementary Note 4). The electrochemical surface areas (ECSA) of LC-Cu NTs, NRs, and NSs were tested to determine the intrinsic activity of the catalysts before the electrocatalytic deuteration reactions (Supplementary Fig. 14). We observe a much larger reduction peak of 1a from the CV curve of LC-Cu NTs than that of LC-Cu NRs and LC-Cu NSs (Supplementary Fig. 15a). This may hint at a larger amount of 1a adsorbing on the surface of LC-Cu NTs. Additionally, inductively coupled plasma atomic emission spectroscopy (ICP-AES) was used to measure the K⁺ adsorbed away from the electrolytes. Supplementary Fig. 15b shows that the high-curvature structure LC-Cu NTs have the largest electric-field-induced locally absorbed K⁺ concentration, agreeing with the theoretical prediction from the DFT calculation. These results verify the concentrated effect of LC-Cu NTs on nitriles and D₂O. Although the LC-Cu NTs have the smallest ECSA, the highest Conv. of 1a and FE of 2a are obtained under the standard reaction conditions (Supplementary Fig. 15c), confirming the high-curvature structure promoting the electrocatalytic deuteration of 1a. Furthermore, compared with the Cu-H₂ NTs, a remarkable increase in the onset potential is observed, and a more negative potential is also required to achieve a current density of -10 mA cm⁻² from the linear sweep voltammetry (LSV) curves of the deuteration evolution reaction over LC-Cu NTs (Supplementary Fig. 16), showing the poor activity of LC-Cu NTs for D₂ formation. This result suggests that engineering low-coordination sites into Cu can inhibit D₂ formation, thus improving the FE of the electroreduction of nitriles with D₂O. Therefore, the electric field-enhanced concentration of nitriles and D₂O and the low-coordination sites prohibiting D₂ evolution will be helpful to speed up the electrocatalytic deuteration of nitriles by increasing the FE of α,β-DAEPAs, rationalizing our predictions.

Second, the adsorption behavior of 1a on the LC-Cu NTs surface was investigated by in situ Raman spectroscopy. As shown in Fig. 5a, the characteristic Raman bands of pure 1a located at 1615 and 2250 cm⁻¹ are assigned to the C=C vibration (νC=C) of the benzene ring and C≡N vibration (νC≡N), respectively. When introducing the LC-Cu NTs, a clear redshift of νC≡N is observed. This may be ascribed to the oriented parallel adsorption of the C≡N group on the LC-Cu NTs surface, as demonstrated by the Tian group.⁴⁵ The peak of the C=C bond vibration of the benzene ring becomes wider with moving toward the low wavenumber, suggesting adsorption on LC-Cu NTs. Meanwhile, the intensity of νC≡N and νC=C first increases, which may be due to the field-effect enhanced concentration of 1a, and then decreases owing to the conversion of 1a as the electrolysis proceeds. However, we do not observe obvious adsorption of the imine intermediate and amine product by the in situ Raman tests, which may be ascribed to the higher activity of imine due to its fast deuteration and the weak adsorption of amine 2a. Third, we used electron paramagnetic resonance (EPR) measurements to detect the possible radical intermediates during electroreductive deuteration of 1a with D₂O by using 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) as the trapping agent (Fig. 5b and Supplementary Note 5). The results show the characteristic hyperfine structure signals of DMPO-D spin adducts (marked by *) that form during cleavage of the D-OD bond and
the signals of DMPO-C (marked by #) during the conversion of 1a. Importantly, the spin adducts of DMPO-D and DMPO-C are further confirmed by high-resolution mass spectrum (HR-MS) tests (Figs. 5c-e and Supplementary Note 6), which have been reported before. However, no information related to the deuterated imine intermediate is found in the HR-MS spectrum.

Based on the experimental results above, a possible reaction mechanism for the one-pot synthesis of α,β-DALLEPs from AANs and D$_2$O is proposed by selecting 1a as the substrate model (Fig. 5f). A quick H/D exchange of 1a with D$_2$O with the assistance of K$_2$CO$_3$ proceeds in the bulk solution to generate α-deuterated 1a (denoted α-D-1a). When electrolysis begins, α-D-1a and hydrated K$^+$(D$_2$O)$_n$ are concentrated and adsorb on the LC-Cu NTs surface due to the high-curvature structure, which enhances the electric fields along the tips. Then, electroreductive deuteration of α-D-1a via a stepwise D radical addition process (α-D-1a→I→imine II→III→2a) generates the deuterated primary amine product. Finally, 2a desorbs from the surface of LC-Cu NTs to release the catalytic sites for the next reaction cycles. However, we cannot fully rule out a proton-coupled electron transfer process for this reaction, which is often put forward in the electrochemical hydrogenation or deuteration of unsaturated compounds.$^{21,30,46}$ Moreover, the reaction pathways and potential energy profiles for electrocatalytic hydrogenation (for simplifying the simulations) of 1a over LC-Cu NTs were provided according to our proposed mechanism. Supplementary Fig. 17 reveals that 1a is more easily absorbed on the LC-Cu surface than on CS-Cu, which further proves that the low-coordination structure contributes to enhancing the adsorption of organic reactants. In addition, the energy barrier for further hydrogenation of the imine intermediate is much smaller than that of 1a (0.17 vs. 0.04 eV) for LC-Cu. This suggests that the hydrogenation of C=N is much easier than that of C≡N, accounting for the unsuccessful detection of the imine intermediate during reductive deuteration of 1a by in situ Raman and HR-MS. Moreover, the desorption energy of 2a from LC-Cu is smaller than that of Cu (1.55 vs. 1.70 eV), indicating the easier desorption of 2a.

Methodology universality.

The general applicability of the one-pot deuteration for the synthesis of α,β-DALLEPs from nitriles and D$_2$O is tested (Table 1). A series of aryl acetonitriles with both electron-withdrawing and electron-donating substituents on the aryl rings are amenable to our strategy, giving rise to α,β-DALLEPs with good to high isolated yields and excellent α- and β-D ratios (2a-l). To be delighted, the active hydrogen of the -OH and -NH$_2$ groups on the aryl ring exerts no noticeable influence on the D ratios of the deuterated products (2b and 2c). Substrates containing O- and N-heterocycles or having a large steric hindrance work well to deliver the desired product with high yields and D ratios (2m and 2n). Additionally, 2-phenylpropanenitrile and 3-butoxypropanenitrile are also good candidates to give the α,β-deuterated amines 2o and 2p with high reaction efficiencies. Furthermore, the aromatic nitriles can also be deuterated under our reaction conditions, and α-deuterated amines with satisfactory yields and D ratios are obtained (2q-t). Note that their nondeuterated analogs 2c, 2f, and 2m are important drugs for the treatment of neuropsychiatric disorders,$^{19,20}$ and the introduction of D is anticipated to further improve their bioactive activities. Overall,
our deuteration strategy is well applied to different types of nitrile substrates, including aryl acetonitriles, arylnitriles, and alkylnitriles, for the fabrication of α- and α,β-deuterated primary amines with high yields and D ratios, demonstrating good methodology universality (Supplementary Note 7).

Impressively, our one-pot deuteration approach can be feasibly developed for the scale-up synthesis of α,β-DAEPAs adopting a flow reactor (Fig. 6a). In addition, 0.90 g of 2i and 0.89 g of 2u are facilely synthesized (Supplementary Note 8), demonstrating the potential utility of our method. By using 1i as the starting material, D-incorporated d₄-tetrabenazine with a 55% overall yield is synthesized for the first time according to reported procedures (Fig. 6b, Supplementary Note 9). The D installed at the N-heterocycle of tetrabenazine may provide an alternative to further enhance the activity and metabolic stability of tetrabenazine for the treatment of chorea associated with Huntington’s disease, which is expected to make an important complement to the deutetrabenazine (Austedo™) that bears −OCD₃ moieties.7

It is well documented that melatonin has decent therapeutic effects on breast cancer, especially estrogen receptor (ER)-positive types.49,50 Therefore, typical ER-positive MCF-7 breast cancer cells were chosen to evaluate the anti-proliferation effect of d₄-melatonin, which is fabricated from the obtained 2u (Supplementary Note 10). Through flow cytometry analysis, both melatonin and d₄-melatonin induced evident apoptosis of MCF-7 cells after 24 h of treatment (Fig. 6c and Supplementary Note 11). Of note, the apoptosis ratio of d₄-melatonin-treated cells was more significant than that of the cells treated with melatonin, indicating the enhanced antitumor effect of melatonin after deuteration. However, the antioxidation capability of melatonin may severely limit its application because melatonin is easily oxidized by in vivo reactive oxygen species (ROS) and loses pharmaceutical activity.49,50 Thus, the antioxidant evaluation of d₄-melatonin is conducted using X-ray-irradiated NIH3T3 cells, which are abundant with ROS. Both CLSM images and flow cytometry analysis reveal that normal melatonin indeed possesses an obvious ROS scavenging capacity while no significant difference in the intracellular ROS level is found between the d₄-melatonin group and the PBS group (Fig. 6d). This circuitously proves that d₄-melatonin is difficult to oxidize in biological tissues, pointing to a superb potential for its clinical transformation. These results further confirm that elaborately incorporating D into drugs may effectively improve the bioactivity and/or the pharmacokinetic stability to make them more feasible for in vivo applications, highlighting the significance of deuteration in drug design and development.

Finally, the LC-Cu NTs are also applicable to the electrocatalytic reductive deuteration of other groups, such as C−I, C≡C, C=O, and NO₂ (Supplementary Fig. 18), with higher Conv. and FE than the LC-Cu NRs and LC-Cu NSs, further demonstrating the general applicability of the high-curvature structure with abundant low-coordination sites in promoting the deuterated synthesis using D₂O.

Conclusion
The increased electric fields of the tips are theoretically predicted to concentrate nitriles and K+ (D2O)n, and low-coordination sites promote nitriles and D2O adsorption for facilitating nitrile deuteration from D2O with an improved reaction rate. The higher coupling energy barrier of active hydrogen atoms at low-coordination sites restricts the D2 evolution to increase FE. Therefore, these factors make one Cu material with a tip structure and low-coordination surface a good candidate for accelerating the electrocatalytic hydrogenation of nitriles with a high reaction rate and Faradic efficiency. Then, LC-Cu NTs with high-curvature nanotip and low-coordinated Cu sites are designedly synthesized from the electroreduction method of CuO nanotip precursors. LC-Cu NTs allow a one-pot H/D exchange with electrocatalytic reductive deuteration of C≡N to synthesize α,β-DAEPAs with up to a Faradic efficiency of 90% and a reaction rate of 0.11 mmol h⁻¹ cm⁻², greatly outperforming corresponding Cu nanorods/nanosheets and other reports. The CV and ICP-AES tests confirm that LC-Cu NTs can concentrate nitriles and hydrated K+, which accelerates the deuteration of nitriles. The LC-Cu NTs display a worse performance for D2 evolution than the Cu-H2 NTs from the LSV curves, which is favorable to improve the FE of the electroreductive deuteration of nitriles. Additionally, a stepwise D radical addition process is proposed, and the D and important carbon radical intermediates are confirmed by EPR and HR-MS. Furthermore, a variety of aryl acetonitriles bearing different functional groups on the different positions of the aryl rings, arylnitriles, and alkylnitriles work well under the determined reaction conditions, giving the α- and α,β-deuterated primary amines with high yields and D ratios. Gram-scale synthesis of α,β-DAEPAs and successful construction of the deuterated drugs d4-tetrabenazine and d4-melatonin are accomplished. Moreover, d4-melatonin exhibits decent therapeutic effects on breast cancer and antioxidant properties, manifesting the important roles of deuterium for drug development. Furthermore, the LC-Cu NTs can also be applied to other electrocatalytic deuteration reactions to significantly improve the reaction rates and FEs, demonstrating good generality. Our work not only offers a facile and efficient strategy for the synthesis of α,β-deuterated aryl primary amines with high FE, reaction rate, and deuterium ratios but also offers a paradigm for designing and synthesizing nanomaterials with low-coordination and high-curvature structures to improve the intrinsic activity and selectivity of other organic electrocatalytic transformations.

**Methods**

**Synthesis of CuO nanotips (NTs).** The self-supported CuO NTs were synthesized by the wet chemical process according to the reported work with a slight change. First, the commercial Cu foam was ultrasonically treated with acetone, 3.0 M HCl solution, and deionized water (DIW) for 15-20 min, respectively. Then, the treated copper foam was immersed in an aqueous solution of 2.0 M sodium hydroxide and 0.15 M ammonium persulfate for 7 min without stirring. After that, the Cu foam covered with the blue Cu(OH)2 NTs was removed from the solution, washed with DIW and absolute ethanol, and dried at room temperature. Finally, the Cu(OH)2 NTs/Cu foam was put into a porcelain boat, heated at 150 °C for 2 h at a heating rate of 1 °C/min and cooled to room temperature to obtain the CuO NTs.
In situ electroreduction of CuO NTs to low-coordinated Cu NTs (LC-Cu NTs). The LC-Cu NTs were in situ synthesized via electroreduction of CuO NTs in a divided three-electrode system using 0.5 M K$_2$CO$_3$ solution as the electrolyte at -1.0 V vs. Hg/HgO for 30 min to ensure the complete disappearance of the reduction peak. The as-prepared CuO NTs with an exposed surface area of 1.0 cm$^2$ served as the working electrode, a carbon rod was used as the counter electrode, and Hg/HgO was used as the reference electrode.

**Characterizations.** Scanning electron microscopy (SEM) images were taken with an FEI Apreo S LoVac scanning electron microscope (1 kV). Transmission electron microscopy (TEM) images were obtained with a FEI Tecnai G2 F20 microscope. The X-ray diffraction (XRD) patterns of the products were analyzed in the range of 10° to 90° at a scan rate of 20° min$^{-1}$ using a Rigaku Smartlab9KW diffraction system with a Cu Kα source ($\lambda = 1.54056$ Å). X-ray photoelectron spectroscopy (XPS) measurements were performed on a Thermo Fisher ESCALAB-250Xi photoelectron spectrometer using a monochromatic Al Kα X-ray beam (1486.60 eV). All the peaks were calibrated with the C 1s spectrum at a binding energy of 284.8 eV. The X-ray absorption spectra (XAS), including X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS) of the Cu K-edge, were undertaken under an ultra-high vacuum at the 1W1B beamline of the Beijing Synchrotron Radiation Facility (BSRF). The XAS spectra were analyzed with the ATHENA software package. The NMR spectra were recorded on a JEOL JNM-ECZ400S/L1 instrument at 400 MHz ($^1$H NMR) and 101 MHz ($^{13}$C NMR) with DMSO-$d_6$ and CDCl$_3$ as the solvents. Chemical shifts were reported in parts per million (ppm) downfield from internal tetramethylsilane. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), br (broad). Coupling constants were reported in hertz (Hz). The quantitative analysis of the liquid products was conducted by a gas chromatograph (GC, Agilent 7890A) with thermal conductivity (TCD), flame ionization detector (FID), and HP-5MS capillary column (0.25 mm in diameter, 30 m in length). Identification of the reactants and products was performed using gas chromatography-mass spectrometry (Agilent, 8860GC-5977MS) with an HP-5MS capillary column (0.25 mm in diameter, 30 m in length). The injection temperature was set at 300 °C. Nitrogen was used as the carrier gas at 1.5 mL min$^{-1}$. Accurate mass measurements of products were obtained via high-resolution mass spectrometry (HR-MS, ESI, positive mode) on an Agilent 6550 QTOF. Hydrogen and carbon radicals were investigated with electron paramagnetic resonance (EPR) spectroscopy (JES-FA200, JEOL, Japan).

**Electrochemical measurements.** The electrochemical deuterated measurements were carried out in a divided three-electrode electrochemical cell separated by the membrane. The as-prepared catalyst was taken as the working electrode, a carbon rod was used as the counter electrode, and Hg/HgO was used as the reference electrode. 0.5 M D$_2$O solution of K$_2$CO$_3$ (6.0 mL) was added to the cathodic and anodic cells, respectively. Then, 0.1 mmol of reactants dissolved in 1 mL of Diox was added into the cathodic cell under stirring (600 rpm) to form a homogeneous solution, and chronoamperometry was carried out at -1.3 V. (All the potentials in this work were referred to Hg/HgO without iR correction unless otherwise stated.) After the reaction was finished, 0.05 mmol of dodecane was added to the reaction system as the internal standard substance. Then, the solution at the cathodic cell was extracted with dichloromethane (DCM) and dried with anhydrous Na$_2$SO$_4$. The DCM was removed, and the products were tested by GC to
calculate the Conv. of nitriles and Sele. of amine products. In addition, the organic phase was treated with 3.0 M cyclopentyl methyl ether hydrochloric acid solution, and the precipitated solid product was filtered to calculate the isolated yields of the products, which were further subjected to NMR testing. Conv., Sele., and FE (1a and 2a as examples) were determined using dodecane as an internal standard and calculated using equations (1) - (4) below. The deuterated ratios of the deuterated products were determined by $^1$H NMR according to equations (5) - (6).

\[
\text{Conv.} \, (\%) = \frac{n \text{ (consumed substrates)}}{n \text{ (initial substrates)}} \times 100\% \quad (1)
\]

\[
\text{Sele.} \, (\%) = \frac{n \text{ (obtained substrates)}}{n \text{ (consumed substrates)}} \times 100\% \quad (2)
\]

\[
\text{Yield} \, (\%) = \frac{n \text{ (obtained products)}}{n \text{ (theoretically formed products)}} \times 100\% \quad (3)
\]

\[
\text{FE} \, (\%) = \frac{4 \times n \times 96480}{Q \text{ (actual values)}} \times 100\% \quad (4)
\]

Deuterium incorporation at $\alpha$-position (\%)

\[
= 100\% - \frac{\text{area (R-CH}_2\text{-CD}_2\text{-NH}_2\text{·HCl)}}{2} \times 100\% \quad (5)
\]

Deuterium incorporation at $\beta$-position (\%)

\[
= 100\% - \frac{\text{area (R-CD}_2\text{-CH}_2\text{-NH}_2\text{·HCl)}}{2} \times 100\% \quad (6)
\]

**In situ Raman spectroscopy.** Raman spectroscopy was performed on the aforementioned Renishaw inVia reflex Raman microscope under an excitation of 532 nm (for LC-Cu catalyst) or 633 nm (for the organic reactant) laser by using an in situ electrochemistry method. The electrolytic cell was made up of Teflon with a piece of round quartz glass as the cover to protect the objective. The working electrode was set to keep the plane of the sample perpendicular to the incident laser. Pt wire was used as the counter electrode, and Hg/HgO was used as the reference electrode. A mixed solution of Diox/0.5 M K$_2$CO$_3$ with 0.1 mmol 1a was added to the cathodic cell. The Raman spectra were recorded by using chronoamperometry at -1.3 V.

**Declarations**

**Data availability**

The data that support the plots within this paper are available from the corresponding author upon reasonable request. The source data underlying Figs. 2-5 are provided as a Source Data file. Source data
are provided with this paper.

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Author contributions

B.Z. and C.L. conceived the idea and directed the research. M.H., C.L., and B.Z. designed the experiments. M.H. and R.L. synthesized the materials and carried out the electrochemical experiments. M.H., R.L., and C.L. analyzed the NMR data. C.C. contributed to the density functional theory calculations. L.Y. carried out the drug activity experiment. M. and Y.W. helped to isolate the products and perform the NMR tests. C.L. wrote the paper. B.Z. revised the paper with comments from all authors.

Competing interests

The authors declare no competing interests.

References


**Table**

Table 1 is available in the Supplementary Files section

**Figures**
a. Deuteration in drug design: Pharmacologically active deuterated molecules

- **Austedo™**
  - Treatment of Huntington’s disease
  - FDA approved first deuterated drug
  - 2013

- **CTP-692**
  - Treatment of Schizophrenia
  - Phase II clinical trial
  - 2017

- **α6-clopidogrel**
  - Inhibitory activity of platelet aggregation
  - 2019

- **SD-1077**
  - Treatment of Parkinson’s disease
  - Phase I clinical trial
  - 2021

b. Typical two-pot methods for the synthesis of αβ-DAEPAs

\[
\begin{align*}
    \text{Ar-CN} & \xrightarrow{\text{NaOD-D}_2\text{O, MeOD, or CDCl}_3} \text{Ar-CN} \\
    & \xrightarrow{\text{NaBD}_4, \text{LiAlD}_4, \text{or} \ D_2} \text{Ar} \text{-NH}_2 \\
    & \text{Separated}
\end{align*}
\]

c. Our one-pot tandem strategy for the synthesis of αβ-DAEPAs

\[
\begin{align*}
    \text{Ar-CN} & \xrightarrow{\text{K}_2\text{CO}_3/\text{D}_2\text{O}} \text{LC-Cu NTs} \\
    & \xrightarrow{\text{Fast} \ H/D \ exchange} \text{Efficient} \ \text{electroreductive} \\
    & \xrightarrow{\text{deuteration}} \text{Ar} \text{-ND}_2
\end{align*}
\]

- Enhanced concentration and adsorption
- High D ratio, FE, and reaction rate
- Wide substrate scope
- Gram-scale synthesis
- Biological activity test

Figure 1

Schematic comparison of the synthesis of αβ-DAEPAs. **a** Representative examples of aryl ethylamine-related drugs. **b** Typical methods and **c** Our one-pot two-step deuteration strategy for the synthesis of αβ-DAEPAs.
Figure 2

Consideration factors and calculation results for an efficient candidate for electroreductive deuteration of nitriles. 

a) Electroreductive deuteration of nitriles with a competitive deuterium evolution reaction. b) Electrostatic field on the surface of different Cu-based catalysts. The tip radiuses of the structures are 50 nm (left) and 5 nm (right), respectively. c) Surface K⁺ density distributions on the surface of Cu NTs. d) Comparison of the d band centers of CS-Cu and LC-Cu. e) The adsorption energy of CH₃C≡N (red) and
CH$_3$C=N (blue) over CS-Cu and LC-Cu, respectively. f The adsorption energy of CH$_3$CH$_2$NH$_2$ over CS-Cu and LC-Cu. g The free energy for the water-splitting process over CS-Cu and LC-Cu.

Figure 3

Synthesis and characterization of LC-Cu NTs via electroreduction of CuO NTs. a The synthesis of self-supported LC-Cu NTs via an in situ electroreduction strategy. b SEM image of LC-Cu NTs. c In situ Raman spectra of LC-Cu NTs collected at -1.0 V in 0.5 M K$_2$CO$_3$. d XRD patterns of CuO NTs and LC-Cu NTs. e Cu 2p XPS spectra of CuO and LC-Cu NTs. f Cu K-edge XANES spectra. g 2-D contour plots WT of LC-Cu NTs and Cu foil, and h EXAFS spectra.
Figure 4

Performances of one-pot synthesis of α,β-DAEPAs in D₂O. a CV curves of LC-Cu at a scan rate of 3 mV s⁻¹ in Diox/0.5 M K₂CO₃ (1:6 v/v, 7 mL) with and without 1a. Potential-dependent Conv. of 1a and Sele. and FE of 2a over b LC-Cu NTs and c Cu-H₂ NTs. d Time-dependent 1a Conv. and 2a Sele. over LC-Cu NTs. e Durability tests of LC-Cu NTs. Reaction conditions: -1.3 V, a mixed solution of Diox/0.5 M K₂CO₃ (3:4 v/v, 30 mL), RT.
Combining experiments with theoretical calculations for mechanistic studies. a In situ Raman spectra in a mixed solution of Diox/0.5 M K₂CO₃ for the electrocatalytic deuteration of 1a (0.1 mmol) over LC-Cu NTs at -1.3 V. b EPR trapping for deuterium (*) and carbon (#) radicals during the electrochemical experiments over LC-Cu NTs. c-e HR-MS tests of the possible intermediates during electroreductive
deuteration of 1a with D₂O over LC-Cu NTs by adding the trapping agent DMPO. A proposed reaction mechanism.

Figure 6

Methodology applications and biological activity tests of d₄-melatonin. a Gram-scale synthesis of α,β-DAEPAs by using a flow reactor. b The synthesis of d₄-tetrabenazine and d₄-melatonin. c The therapeutic
effects of $d_4\text{-melatonin}$ on breast cancer MCF-7 cells. The antioxidant activity of $d_4\text{-melatonin}$.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- [HMNatNanotechnolSI20230102.pdf](#)
- [Table1.docx](#)