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Unravelling the hidden link of lithium halides and application in the synthesis of organocuprates

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As a versatile metal, copper has demonstrated a wide application in acting as both organometallic reagent and catalyst. Organocuprates are among the most used organometallic reagents in the formation of new carbon-carbon bonds in organic synthesis. Therefore, revealing the real structures of organocuprates in solution is crucial to provide insights into the reactivity of organocuprates. Here we provide several important insights into organocuprate chemistry. The main finding contains the following aspects. The Cu(0) particles were detected via the reduction of CuX by *n*BuLi or PhLi. The Cu(II) precursors CuX₂ (X = Cl, Br) could be used for the preparation of Gilman reagents. In addition, we provide direct evidence for the role and effect of LiX in organocuprate synthesis. Moreover, the EXAFS spectrum provides direct evidence for the exact structure of Li⁺ CuX₂⁻ ate complex in solution. This work not only sheds important light on the role of LiX in the formation of organocuprates but also reports two new routes for organocuprate synthesis.

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Since the pioneering work of Gilman *et al.*,¹ organocuprates have been widely employed as organometallic reagents in organic synthesis (including conjugate additions, the opening of epoxides and cross-coupling reactions)^{2–7}. In the textbook, organocuprates are usually prepared through transmetalation of lithium, magnesium or zinc organometallics with Cu(I) salts⁸. Different coordination environments always drastically affect the reactivity or stabilities of organocuprates⁹. Up to now, a lot of synthetic methodologies involving organocuprate reagents have been developed, while great uncertainty still exists in the related mechanism¹⁰. Although several important crystal structures of organocuprates were reported^{11–14}, it should be noted that solid-state structures often reflect the most thermodynamically stable species and are not necessarily the same as in solution state. Besides, organocuprates can exhibit complex behaviour in solution, often existing as a number of different species in equilibrium, thus further complicating their characterization. For that reason, the structure of organocopper compounds in solution cannot be inferred directly from crystal structures and must be determined independently.

The structures of organocuprate reagents in an ethereal solution have received wide attention, because they are strongly relevant to reactivity in real reaction conditions^{15–17}. Nuclear magnetic resonance^{18–20} and electropray ionization–mass spectrometry^{21,22} served as powerful tools and have been widely used in determining the structures of organocuprates in solution. The linear bonding geometry of the C–Cu–C moiety in cuprates such as MeCu(CN)Li, Me₂CuLi and Me₂CuLi₃LiX (X = I, CN) has been well established. In 1996, Knochel and colleagues^{23,24} first introduced the extended X-ray absorption fine structure (EXAFS) to study the local structure of organocuprates from the reaction between CuCN and *n*BuLi. EXAFS spectroscopy provides a unique probe of the local structural environment of metal ions in non-crystalline systems^{25–33}. The preliminary structure for lithium cyanocuprates based on EXAFS data has been elucidated. However, the role of cyanide and the difference between cyanide and other halide atoms still remain in debate⁹. Lipshutz *et al.*²¹ and Koszinowski and colleagues³⁴ have

pointed out the LiX could have a positive effect on the solubility of CuX (X = I, Br, Cl, CN) independently. The electropray ionization–mass spectrometry was used to study the structure of formed ate complex^{21,34}. However, determination of the exact structure, the role for LiX and application in organocuprates have still been not well-studied up to date. We started our research by investigating the effect of anion on organocuprates preparation. Here we show the anion effect of different Cu(I) precursors on Gilman reagent preparation. The EXAFS reveals that the LiX (X = Br, Cl) serves as the hidden link for organocuprates preparation from unfavoured CuX. A soluble cupric bromide anion intermediate is evidenced by EXAFS when adding LiBr to CuBr in tetrahydrofuran (THF). This CuX₂[−] Li⁺ ate complex serves as a key intermediate in the generation of Gilman reagent (Fig. 1). In addition, we also shed two other important findings in this work. First, the detection of copper nanoparticles produced after the addition of *n*BuLi or PhLi to CuX. Second, the Cu(II) precursors CuX₂ (X = Cl, Br) can be used for the preparation of Gilman reagents.

Results

Detection of Cu(0) particles via the reduction of CuX. In organic synthesis, different Cu(I) precursors are always applied in different reaction systems¹⁰. Initially, we investigated different cuprous salts with excess *n*BuLi in THF under -78°C for organocuprates synthesis. From X-ray absorption near-edge spectroscopy (XANES) spectra (Fig. 2a), we observed the difference of reactions from CuCN and CuX (X = Br, Cl). In Fourier-transformed EXAFS spectra, an obvious copper nanoparticle feature at high shells in CuBr and CuCl complexes appeared (Fig. 2b). However, such peaks at 3.4, 4.1 and 4.8 Å were not detected in the CuCN system, which is accordance with previous literature²³ that CuCN is a good precursor to Gilman reagent. In addition, such results also indicate that organocuprates made by CuBr or CuCl are very unstable to decompose into zero valance copper nanoparticle. Meanwhile, it seemed that the smaller the anion atom is, the more Cu(0) particle is formed.

Then, we also used X-ray absorption spectroscopy (XAS) to study the reaction between CuX (X = Br, Cl) and PhLi. The XANES spectra were shown in Supplementary Fig. 1. From the EXAFS spectra in Fig. 3a, we found that the mixture of Cu(0) and Cu(I) species was formed when mixing CuBr or CuCl with PhLi. The CuCl was easier to be reduced to Cu(0) particle than CuBr by PhLi, which was consistent with the reaction with *n*BuLi. In addition, we also investigated the solvent effect on this process. We found that the reduction process was even faster when using

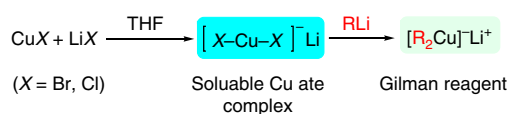


Figure 1 | Hidden link of lithium halides. Scheme of the role of LiX (X = Br, Cl) and application in Gilman reagent preparation.

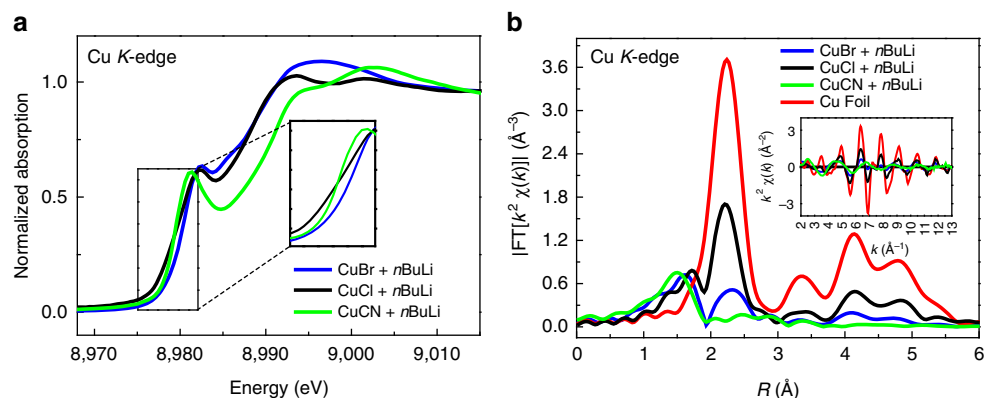


Figure 2 | XAFS analysis of CuX reduction. (a) XANES spectra of various cuprous salts with excess *n*BuLi in THF under -78°C . (b) Comparison of FT magnitudes of k^2 -weighted EXAFS of various Cu(I) species mixed with excess *n*BuLi in THF under -78°C . ($3.0 \text{ \AA}^{-1} < k < 12.4 \text{ \AA}^{-1}$).

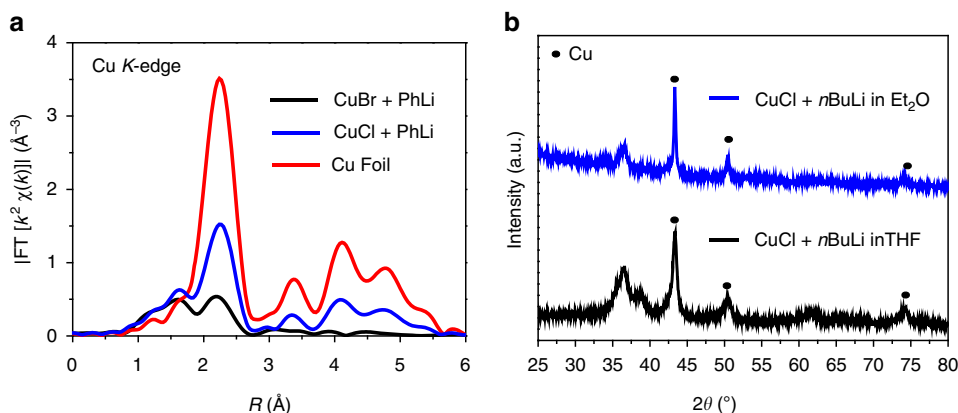


Figure 3 | EXAFS and X-ray powder diffraction analysis. (a) EXAFS spectra of CuBr and CuCl mixed with excess PhLi in THF under $-78\text{ }^{\circ}\text{C}$. (b) X-ray powder diffraction experiments, blue line: CuCl + 5.0 equiv *n*BuLi in Et₂O, black line: CuCl + 5.0 equiv *n*BuLi in THF.

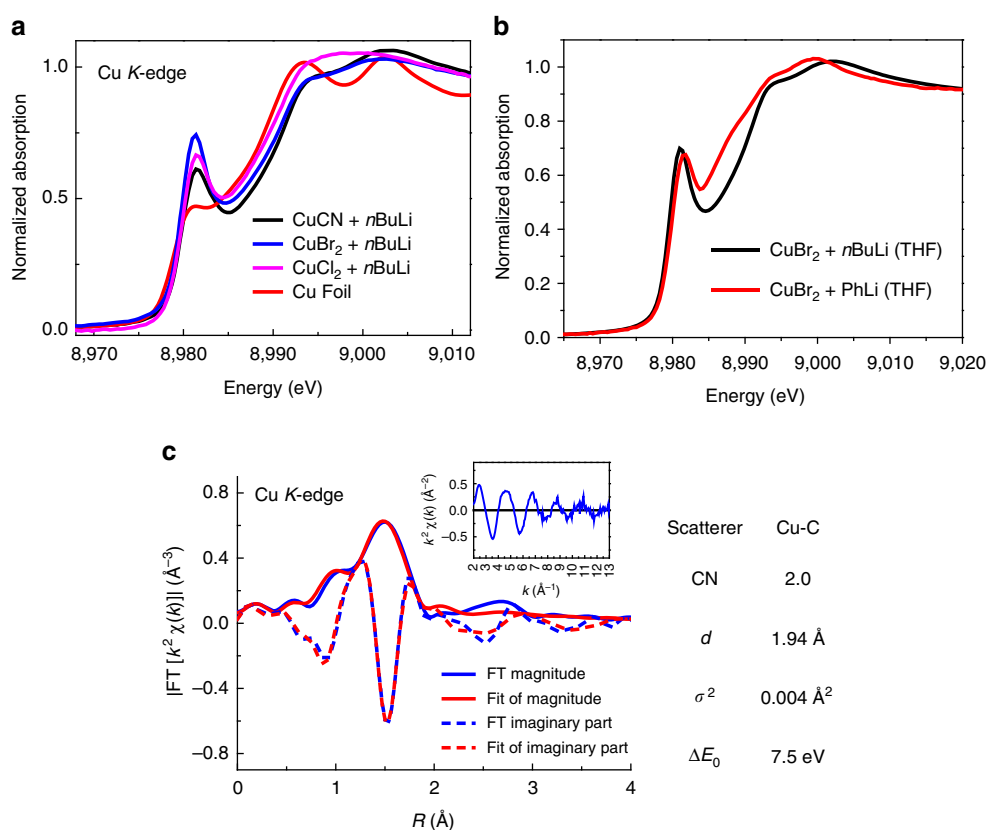


Figure 4 | XAFS analysis of CuX₂ reduction. (a) XANES spectra of CuCN, CuBr₂ and CuCl₂ mixed with excess *n*BuLi in THF under $-78\text{ }^{\circ}\text{C}$. (b) XANES spectra of CuBr₂ mixed with excess PhLi in THF under $-78\text{ }^{\circ}\text{C}$. (c) Fitting result for CuBr₂ + 5.0 equiv *n*BuLi in THF solution ($2.910\text{ }^{\circ}\text{Å}^{-1} < k < 11.472\text{ }^{\circ}\text{Å}^{-1}$ and $1.065\text{ }^{\circ}\text{Å} < R < 2.127\text{ }^{\circ}\text{Å}$).

ethyl ether (Et₂O) as the solvent (Supplementary Figs 2 and 3). To further evidence the Cu(0) species and this reduction process, X-ray powder diffraction experiments were performed and the results are shown in Fig. 3b. The figure shows the main existence of Cu in the reaction between CuCl and *n*BuLi in THF or Et₂O, in which the three peaks at 43.3°, 50.4° and 74.1° are corresponding to the (111), (200) and (220) planes of Cu (JCPDS number 04-0836), respectively.

Reduction of Cu(II) precursors. As the *n*BuLi could serve as a reductant to reduce CuX (*X* = Br, Cl) to Cu(0) species, we also employed EXAFS to investigate the reactions between Cu(II) salts

and *n*BuLi. We are very excited to discover that instead of using Cu(I) as the starting reagent, more stable and cheaper Cu(II) halide salts could also be good Gilman reagent precursors in the presence of excess organolithium reagent. EXAFS provided us a direct view of these transformations. Compared with traditional Gilman reagent prepared from CuCN, we could see that in the presence of 5.0 equivalent of *n*BuLi in THF under $-78\text{ }^{\circ}\text{C}$, both CuBr₂ and CuCl₂ were reduced into Cu(I) with edge energies about 8979.9 and 8980.0 eV, respectively, in the XANES spectra (Fig. 4a). The PhLi could also reduce CuBr₂ to corresponding Cu(I) species (Fig. 4b). The fitting result further verified the existence of 2-coordinated [C-Cu(I)-C] short-range structure (Fig. 4c). Owing to the fact that CuX₂ is stable and easy to store,

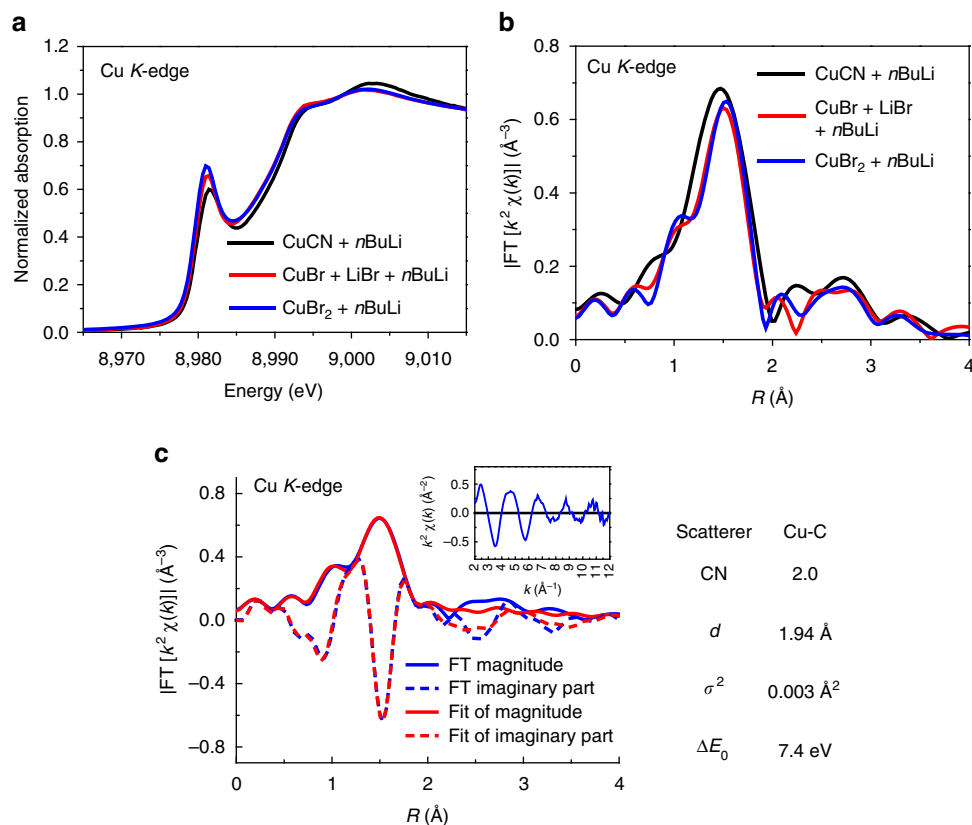


Figure 5 | Role of lithium halides in the synthesis of organocuprates. (a) XANES spectra of CuCN (black), CuBr + 1.0 eq LiBr (red) and CuBr₂ (blue) with excess *n*BuLi in THF under -78°C . (b) EXAFS spectra of CuCN (black), CuBr + 1 eq LiBr (red) and CuBr₂ (blue) with excess *n*BuLi in THF under -78°C . (c) Fitting results of *R*-space k^2 -weighted EXAFS spectra of CuBr + 1 equiv LiBr in 5.0 equiv *n*BuLi THF solution ($2.957 \text{ \AA}^{-1} < k < 11.145 \text{ \AA}^{-1}$ and $1.172 \text{ \AA} < R < 1.914 \text{ \AA}$).

this method will be a new route for organocuprates preparation from CuX₂. We also applied this method to organic synthesis. When adding the electrophile such as benzyl bromide or (2-bromoethyl)benzene into the reaction system, the desired C–C bond formation was formed, which implied that this method for organocuprates could be used for cross-coupling reactions. The detail application of this method in complicated molecular synthesis is on the way in our lab.

Role of lithium halides in the synthesis of organocuprates.

The lithium salts may have an effect on the formation of organocuprates, which has been awaked by several groups^{21,34–39}. Although knowing this phenomenon for a long time, determination of the exact structure, the role for LiX and application in organocuprates have still been not well researched. When one equivalent LiBr was added to the mixture of CuBr and 5 equivalent *n*BuLi, we obtained a similar XANES spectra of which obtained from CuCN and excess *n*BuLi under low temperature (Fig. 5a). The edge energy was determined as 8979.7 and 8979.9 eV, respectively. Furthermore, high shell features for copper nanoparticle disappeared in the EXAFS spectrum, which indicates the formation of relatively pure organocuprate compound (Fig. 5b). The results of fitting show two carbon atoms at 1.94 Å around the copper atom equally (Fig. 5c). Thus, we developed a new method of preparing Gilman reagents using CuX with the help of LiX, which is very similar to what we get from mostly used cuprous cyanide in traditional synthesis route.

To further elucidate the role of LiX in preparing Gilman reagent, the mixture of LiBr and CuBr in THF was used

for demonstration. As shown in Supplementary Fig. 4, the CuBr species alone look polymer-like and very insoluble in THF. In contrast, CuBr can be dissolved in THF with the aid of one equivalent quantity of LiBr. A green solution is quickly formed after adding 1 equivalent LiBr into the system. This result indicated that the CuBr has an interaction with LiBr and a new copper species is possibly formed. The interaction between CuBr and LiBr might be the key to stabilizing the Gilman reagents prepared through this method. Valence alternation in cuprous bromide was invisible in the presence of LiBr from XANES spectra (Fig. 6a, edge energy of 8980.9 eV). In addition, EXAFS fitting results indicate two bromine atoms coordinated to the copper(I) centre (Fig. 6b). Thus, we claim that this type of ate complex was a [Br–Cu–Br][−] Li⁺ anion. This [CuBr₂][−] ate complex shows good solubility and serves as a key intermediate in the generation of Gilman reagent.

Density functional theory calculations. Density functional theory calculation was also performed to provide support for the EXAFS fitting results. As shown in Fig. 7a, the coordination of THF to [Br–Cu–Br][−] anion is endergonic by 6.6 kcal mol^{−1}. The optimized structure suggests that the Cu–O distance is 3.62 Å, which means the interaction between Cu and O is very weak. As previous reports, the monomer state of organocuprates was always present in more polar solvent such as THF. Thus, the monomer structure of organocuprate was calculated. Meanwhile, the coordination of THF to [*n*Bu–Cu–*n*Bu][−] anion is found to be endergonic by 9.9 kcal mol^{−1} and the corresponding Cu–O distance is determined to be 4.43 Å (Fig. 7b). Thus,

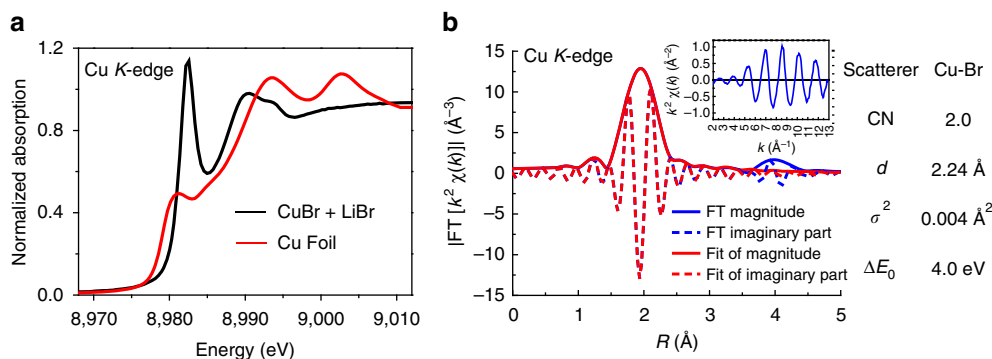


Figure 6 | XAFS analysis of reaction between CuX and LiX. (a) XANES spectra of CuBr + LiBr in THF species. (b) Fitting results of k^2 -weighted R -space EXAFS spectra of CuBr + 1.0 equiv LiBr ($2.890 \text{ \AA}^{-1} < k < 12.134 \text{ \AA}^{-1}$ and $1.487 \text{ \AA} < R < 2.376 \text{ \AA}$).

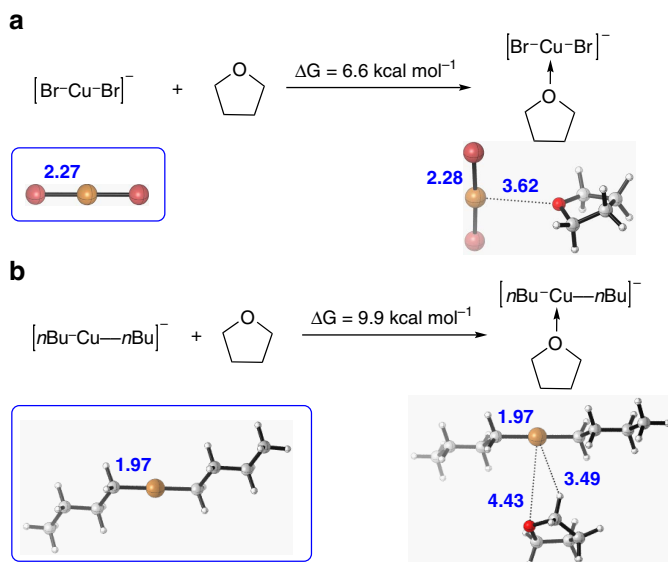


Figure 7 | Density functional theory calculation. Density functional theory calculation for the coordination of THF to (a) $[\text{Br-Cu-Br}]^-$ anion and (b) $[\text{nBu-Cu-nBu}]^-$ anion.

the coordination of THF to $[\text{Br-Cu-Br}]^-$ and $[\text{nBu-Cu-nBu}]^-$ anion are both energetically unfavourable^{19,20,40}. Moreover, optimized structures reveal that the bond length of Cu-Br in $[\text{Br-Cu-Br}]^-$ anion is 2.27 Å and the bond length of Cu-C in $[\text{nBu-Cu-nBu}]^-$ anion is 1.97 Å, which are very close to that obtained from EXAFS (2.24 and 1.94 Å). Consequently, the theoretical study and EXAFS fitting results have reached the same conclusion.

Discussion

To sum up, we elucidate LiX ($X = \text{Br}, \text{Cl}$) as a hidden link in the preparation of organocuprate reagents from CuX ($X = \text{Br}, \text{Cl}$) with a key intermediate $\text{CuX}_2^- \text{Li}^+$ ate complex evidenced by EXAFS. Meanwhile, this Cu(I) ate complex can serve as a good precursor to prepare Gilman reagents following a tandem process. In addition, we also developed the organocuprate reagents synthesis from Cu(II) precursors. This discovery might help open a new perspective in understanding the organocuprate chemistry and mechanisms of copper-catalysed reactions as well.

Methods

General information. X-ray absorption measurements were acquired in transmission mode at beamline 17C1 at National Synchrotron Radiation Research

Center in Taiwan. A pure Cu foil spectrum (edge energy 8979 eV) was acquired simultaneously with each measurement for energy calibration. Multiple scans were taken to reduce the noise. The Supplementary Tables 1–3 revealed the detailed parameters of the XAFS spectral.

Reaction system. Cu salt (0.5 mmol) was added to the schlenk tube cell in a glovebox beforehand. Then, 5.0 ml of THF was injected into the cell and the solution was stirred under N_2 at -78°C for 20 min. Subsequently, RLi (2.5 mmol) was added into the system and stirred for 30 min. As the last step, the liquid nitrogen was quickly added to reaction system, which would be frozen into solid immediately, and it was transferred into the XAFS cell with the protection of nitrogen gas.

Detection system (beamline). The detection system was cooled using cooled nitrogen gas. The Supplementary Fig. 5 was the picture of cell holder used in the beamline. This hold connected with a liquid nitrogen cooled gas stream. The Supplementary Fig. 6 showed our idea for low-temperature system. We used a gas stream passing through the liquid nitrogen Dewar to cool the system. The temperature could be controlled by the tuning of the flow rate. The Supplementary Fig. 7 was the whole picture of experimental set-up in beamline.

Data availability. Data supporting the findings of this study are available within this article and its Supplementary Information file and from the corresponding authors on reasonable request.

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Author contributions

H.Y. and A.L. conceived the project. H.Y., D.Y., X.J., D.Y., C.-W.P. and J.-F.L. performed the experiments, analysed the data and discussed the results. X.Q. and Y.L. performed the density functional theory calculations. H.Y., D.Y. and A.L. wrote the paper. H.Y. and D.Y. wrote the Supplementary Information and contributed other related materials. H.Y. and D.Y. contributed equally to this work. All the authors checked the manuscript.

Additional information

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