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Multiple neighboring active sites of an atomically precise copper nanocluster catalyst for efficient bond-forming reactions†

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Atomically precise copper nanoclusters (NCs) are an emerging class of nanomaterials for catalysis. Their versatile core-shell architecture opens the possibility of tailoring their catalytically active sites. Here, we introduce a core-shell copper nanocluster (CuNC), [Cu₂₉(S^tBu)₁₃Cl₅(PPh₃)₄H₁₀]⁺BuSO₃⁻ (S^tBu: *tert*-butylthiol; PPh₃: triphenylphosphine), Cu₂₉NC, with multiple accessible active sites on its shell. We show that this nanocluster is a versatile catalyst for C-heteroatom bond formation (C–O, C–N, and C–S) with several advantages over previous Cu systems. When supported, the cluster can also be reused as a heterogeneous catalyst without losing its efficiency, making it a hybrid homogeneous and heterogeneous catalyst. We elucidated the atomic-level mechanism of the catalysis using density functional theory (DFT) calculations based on the single crystal structure. We found that the cooperative action of multiple neighboring active sites is essential for the catalyst's efficiency. The calculations also revealed that oxidative addition is the rate-limiting step that is facilitated by the neighboring active sites of the Cu₂₉NC, which highlights a unique advantage of nanoclusters over traditional copper catalysts. Our results demonstrate the potential of nanoclusters for enabling the rational atomically precise design and investigation of multi-site catalysts.

New concepts

In the realm of modern synthetic chemistry, the focus is on developing efficient catalysts with well-defined active sites. Nanostructured materials, like metal nanoparticles, show promise, but their ill-defined structure hinders mechanistic understanding. Atomically precise nanoclusters (NCs), especially copper nanoclusters (CuNCs), with defined structures, offer a solution. Earth-abundant and cost-effective, CuNCs are emerging materials for sustainable catalysis applications. This work introduces a novel core-shell copper nanocluster, Cu₂₉NC, with a unique shell structure, demonstrating its efficiency in diverse C-heteroatom (C–O, C–N & C–S) bond-forming reactions. Unlike previous CuNCs, Cu₂₉NC serves as a recyclable and external ligand-free catalyst for a broad range of reactions, including late-stage functionalization of complex organic molecules. Experimental and theoretical investigations provide insights into its multi-site catalytic mechanism. We anticipate that the new insights gained from this study will be instrumental in the design, synthesis, and applications of more effective nanocluster catalysts for challenging bonding-forming reactions.

Introduction

Carbon-heteroatom (C-heteroatom) bond-forming reactions have played a pivotal role in organic transformations for the synthesis of pharmaceutical compounds, natural products, and organic materials.^{1–7} Pd-catalyzed Buchwald–Hartwig reactions are among the most efficient methods for C-heteroatom cross-couplings.^{8–11} However, the high cost of the metal as well as ligands hampers their widespread catalytic applications.^{8,12} Accordingly, the copper-mediated Ullmann–Goldberg protocol¹³ was devised as a potential cost-effective alternative but often suffered from the usage of stoichiometric amounts of copper and high reaction temperatures (> 150 °C).^{14,15} More recently, the groups of Buchwald,^{16,17} Hartwig,¹⁸ and Ma^{19–22} have pioneered the use of copper catalysts with several ligand scaffolds (including neutral to anionic) to facilitate the cross-coupling reaction efficiently with a broader substrate scope.^{23–26} However, as these Cu-catalyzed cross-coupling reactions require

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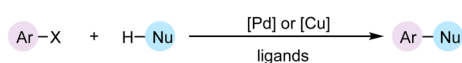
ligands – often in excess amounts^{26–28} – they generate undesired ligand-related waste and may complicate the isolation process. Therefore, there is a pressing need to develop a new catalyst that can demonstrate efficient C-heteroatom coupling reactions without exogenous ligands.

A central objective in modern synthetic chemistry is the development of new and efficient catalysts for challenging bond-forming reactions – catalysts which should also have well-defined multiple active sites and are reusable.^{29–31} Owing to their higher surface area, multiple active sites, and heterogeneous nature, nanostructured materials (*e.g.*, metal nanoparticles, MNPs) have shown great potential for catalytic performance as compared to traditional homogeneous catalysts.^{32–38} However, due to their ill-defined structure it is difficult to delineate the role of active sites in the reaction mechanism and, hence, a catalysis-by-design approach cannot be practically implemented in such systems.³⁹ On the other hand, atomically precise nanoclusters (NCs, <3 nm), featuring well-defined positions of metal and ligands while possessing diverse polyhedral structures,^{39–41} could serve as an ideal catalytic platform to enable the bond-forming reactions with mechanistic understanding owing to their structurally defined multiple active sites and tolerability for recycling. In particular, the catalytic properties of NCs highly depends on the nature of the protecting ligand and motif structure.^{42–45}

To date, the structure–property relationships of nanocluster catalysts have mainly focused on precious metal nanoclusters such as Au and its alloys with Pd, Pt, and Ag for various chemical reactions.^{39,40,43,46} Due to their earth abundance, cost-effectiveness, and versatile ligand architecture, copper nanoclusters have recently emerged for sustainable catalysis of chemical reactions.^{37,47–53} The challenge in the development of new core–shell copper nanoclusters (CuNCs) that facilitate unique bond-forming reactions lies not only in their synthesis, but also in the unravelling of the reaction mechanism through atomically precise structure–property relationships of the CuNCs.

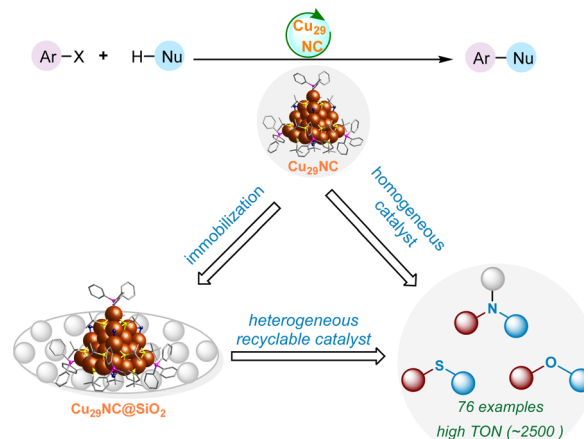
Herein we have designed and synthesized a novel core–shell copper nanocluster, $[\text{Cu}_{29}(\text{S}^t\text{Bu})_{13}\text{Cl}_5(\text{PPh}_3)_4\text{H}_{10}]^+\text{BuSO}_3^-$ (Cu_{29}NC) with a high percentage of chloride ligands on the surface. It encompasses a centred cubooctahedron core (Cu_{13}), shielded by a unique tetrahedral shell, $\text{Cu}_{16}\text{S}_{13}\text{Cl}_5\text{P}_4$. This shell is characterized by three distinct motifs, each exhibiting crown-like structures. The incorporation of chloride ligands in the shell serves to alleviate crowding around the active sites, making it a viable catalyst in organic reactions. We demonstrate that Cu_{29}NC serves as an efficient catalyst to enable the broad range of cross-coupling reactions (C–O, C–N, and C–S) with a high functional group tolerance (Fig. 1). In contrast to previous Cu NCs, such as Cu_{61}NC and Cu_{28}NC , which have proven effective as photocatalysts for certain cross-coupling reactions,^{52,54} this Cu_{29}NC serves as a recyclable external ligand-free catalyst for a broad range of C-heteroatom coupling reactions, including late-stage functionalization of complex organic molecules. A combined experimental investigation (with various controls) with theoretical DFT modeling (based on the single crystal structure) indicate the participation of multiple neighboring metal atoms in all fundamental steps

(a) Conventional catalytic approach for C-heteroatom couplings



- rational ligand design enable C-heteroatom couplings
- acts as a single metal catalysis
- high barrier for [Cu/L]-catalyzed oxidative addition

(b) This work: Cu-nanocluster catalyzed C-heteroatom couplings



- multiple active sites of Cu_{29} enable couplings
- single Cu_{29} catalyst enable various couplings
- heterogeneous recyclable catalyst
- Late-stage functionalization

Fig. 1 Catalytic methods for C-heteroatom bond-forming reactions.

of the reaction. This work opens new avenues for copper nanocluster-based catalysis and sheds light on their catalytic mechanism by DFT calculation based on the single crystal structure.

Results and discussion

Synthesis and characterizations of Cu_{29} nanocluster

The Cu_{29} cluster was synthesized by a two-step procedure. In brief, the reduction of $\text{Cu}(\text{I})\text{-S}^t\text{Bu-PPh}_3$ complex (chloroform solution) by ethanolic solution of sodium borohydride (NaBH_4) produced the Cu_{29}NC . The synthesis procedure is detailed in the experimental section of the ESI.†

A single crystal of appropriate size was used for single-crystal X-ray diffraction (SCXRD). The cluster crystallizes in a triclinic crystal system with $P\bar{1}$ space group (Table S1, ESI†). The total structure of the Cu_{29} clusters derived from the SCXRD is presented in Fig. 2a. A combined study of SCXRD and mass spectrometry confirms the total molecular formula of the cluster, $[\text{Cu}_{29}(\text{S}^t\text{Bu})_{13}\text{Cl}_5(\text{PPh}_3)_4\text{H}_{10}]^+\text{BuSO}_3^-$ (*vide infra*). The cluster contains a centered-cubooctahedron core (Cu_{13} , Fig. 2b and Fig. S1, ESI†) which is protected by a unique tetrahedral shell, $\text{Cu}_{16}\text{S}_{13}\text{Cl}_5\text{P}_4$ (Fig. 2c). The structure contains only one C_1 symmetry axis.

The shell, $\text{Cu}_{16}\text{S}_{13}\text{Cl}_5\text{P}_4$, is composed of three different types of motifs, **motif 1** ($\text{Cu}_4\text{S}_4\text{Cl}_2\text{P}$), **motif 2** ($\text{Cu}_4\text{S}_4\text{Cl}_2\text{P}$), and **motif 3** ($\text{Cu}_4\text{S}_5\text{Cl}_1\text{P}$) (Fig. 2d). All the motifs have crown-like structures. **Motif 1** is connected with two units of **motif 2** through two bridging $\mu_2\text{-Cl}$ whereas **motif 3** is connected to **motif 1** through



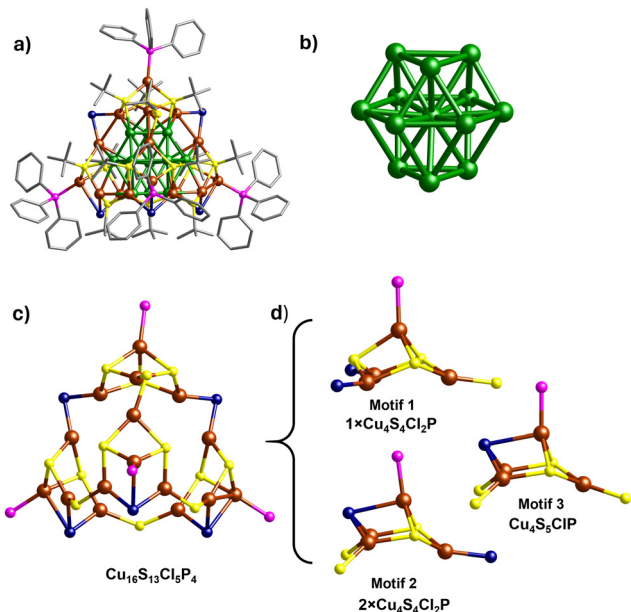


Fig. 2 (a) Molecular structure of $[\text{Cu}_{29}(\text{S}^t\text{Bu})_{13}\text{Cl}_5(\text{PPh}_3)_4\text{H}_{10}]^+$ Cu_{29}NC . (b) Cubo octahedron Cu_{13} core. (c) Structure of tetrahedral shell, $\text{Cu}_{16}(\text{S}^t\text{Bu})_{13}\text{Cl}_5(\text{PPh}_3)_4$. Carbon and hydrogen atoms are omitted for clarity (d) Structures of three distinct types of motifs. Color legend: green, and brown, copper atoms of the Cu_{13} core, and shell, respectively; yellow, sulfur; pink, phosphine; dark blue, chlorine; and gray, carbon.

bridging thiolate ligands. On the other hand, two units of **motif 2** and one unit of **motif 3** are interconnected through three bridging thiolate ligands. The interactions of **motifs 1, 2 and 3** with the Cu_{13} core are quite different. The surface of the Cu_{13} core is composed of six distorted square and eight triangle faces (Fig. S2, ESI[†]). **Motif 1** occupies one of the triangular faces whereas **motifs 2 and 3** occupy the three-square faces of the Cu_{13} core (Fig. S3, ESI[†]). Overall, the Cu_{29}NC occupies a tetrahedral shape where the corners of the tetrahedron are occupied by the triphenylphosphine ligands. Three diverse types of thiolate ligand groups are observed in the Cu_{29}NC (Fig. S4, ESI[†]). Like the thiolate ligands, two types of bridging modes are also observed for the chloride ligands. Two chloride ligands that connect **motif 1** with the two units of **motif 2** have μ_2 bridging mode ($\mu_2\text{-Cl}$) and the remaining three chloride ligands have μ_3 bridging mode ($\mu_3\text{-Cl}$). It is worth mentioning that such kind of chloride rich (high chloride to thiolate ratio) shell structure is rare in the core-shell nanocluster family. The presence of a higher percentage of chloride ions reduces the crowding of surface copper atoms and, hence, heightens their probability of being involved in catalysis.

Generally, copper nanoclusters contain hydrides.^{47,52,55–59} However, it is difficult to locate them using SCXRD for such a larger cluster system. Thus, ESI MS was used to determine the exact composition of the clusters. Details of the sample preparation and instrumental conditions are described in the experimental section of the ESI.[†] Positive mode ESI MS of the chloroform solution of nanoclusters produced a major peak at m/z 4237.8 in the mass range of m/z 20–10000 (Fig. 3). Upon expansion, the peak shows a characteristic separation

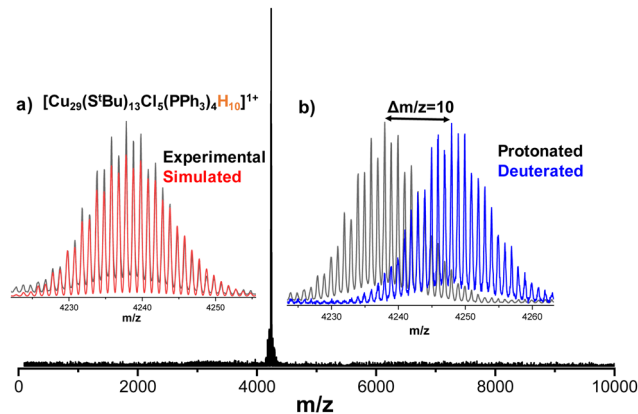


Fig. 3 Positive mode ESI MS spectrum of $[\text{Cu}_{29}(\text{S}^t\text{Bu})_{13}\text{Cl}_5(\text{PPh}_3)_4\text{H}_{10}]^+$ nanocluster. The peak at m/z 4237.8 corresponds to the molecular ion peak. Insets: (a) Exact matching of experimental (black trace) and simulated (red trace) isotopic distributions confirm the assigned compositions. (b) Comparison of protonated, $[\text{Cu}_{29}(\text{S}^t\text{Bu})_{13}\text{Cl}_5(\text{PPh}_3)_4\text{H}_{10}]^+$, and deuterated, $[\text{Cu}_{29}(\text{S}^t\text{Bu})_{13}\text{Cl}_5(\text{PPh}_3)_4\text{D}_{10}]^+$, molecular ion peaks.

of $\Delta m/z = 1$ (Fig. S5, ESI[†]), which confirms the presence of singly charged ($1+$) species. The assigned composition for the above-mentioned peak is $[\text{Cu}_{29}(\text{S}^t\text{Bu})_{13}\text{Cl}_5(\text{PPh}_3)_4\text{H}_{10}]^+$. The exact matching of isotopic distributions of experimental (black trace) and simulated (red trace) spectra confirm the assigned composition (Fig. 3a). Furthermore, to verify the number of hydrides, ESI MS of deuterated analogue of Cu_{29}NC , $\text{Cu}_{29\text{D}}$, was performed. In case of $\text{Cu}_{29\text{D}}$, the peak position is shifted by $\Delta m/z = 10$ due to the replacement of ten hydrogen atoms (m/z 10) by deuterium atoms (m/z 20) which further supports the assigned compositions (Fig. 3b). Similar to the reported copper nanoclusters,^{52,60} we performed geometry optimizations by DFT calculations to locate the ten hydrides (Fig. S6A, ESI[†]). Details of the calculations are presented in the experimental section of the ESI.[†] In order to substantiate the existence of the hydrogen atoms within the NC, a ^2H nuclear magnetic resonance (NMR) analysis was conducted on $\text{Cu}_{29\text{D}}$ in 950 MHz spectrometer in CHCl_3 , as illustrated in Fig. S6B (ESI[†]). These yielded signals originating exclusively from deuterium (D) atoms within the sample and added CDCl_3 for calibration. The resultant NMR spectrum exhibited discernible peaks distributed across a range of chemical shift values, ranging from low to high regions. This observation provides compelling evidence for the presence of deuterium atoms within the NC, indicative of their occupancy in diverse chemical environments.

The unique shell structure along with the easily obtainable clean mass spectrum allowed us to study the cluster further using mass spectrometry (Fig. S7 and S8, ESI[†]). Furthermore, to identify the counter ion, we performed the ESI MS measurement in the negative mode and observed a peak at m/z 137 (Fig. S9, ESI[†]). The exact matching of experimental and simulated isotopic distributions confirms the presence of *tert*-butyl sulfonate ($^t\text{BuSO}_3^-$) as the counter ion, which is in good agreement with SCXRD data (inset, Fig. S9, ESI[†]).

The oxidation state of copper atoms holds a fundamental significance in catalysis, which can influence the reactivity and



selectivity. Thus, we performed X-ray photoelectron spectroscopy (XPS) measurements of the solid powder sample to identify the oxidation states of the copper atoms. XPS survey spectrum presented in Fig. S10a (ESI†) confirms the presence of all the expected elements (Cu, S, Cl, C, and P). High-resolution XPS spectra of Cu 2p, S 2p, C 1s, and Cl 2p are presented in Fig. S10b–e (ESI†). Generally, it is difficult to distinguish Cu(0) and Cu(I) as their 2p binding energy are almost similar. Hence, we gathered Cu LMM Auger spectra of Cu(I)-S^tBu thiolate and Cu₂₉ cluster (Fig. S11, ESI†). The presence of a sharp peak at 916.3 eV confirms that all the copper atoms in Cu₂₉ nanocluster are in +1 oxidation state which is in good agreement with SCXRD and ESI MS analysis.⁶¹ Furthermore, a comparison of Cu LMM Auger spectra Cu(I)-S^tBu thiolate and Cu₂₉ cluster is presented in Fig. S11 (ESI†) which also supports the presence of only Cu(I) oxidation state in Cu₂₉ nanocluster.

Reaction development

We commenced our investigations with the newly synthesized Cu₂₉NC and tested the cluster in the C–O cross-coupling of *p*-bromobenzonitrile and *p*-cresol. Use of 0.05 mol% of catalyst provided 86% of the desired C–O coupled product (Fig. 4 and Table S2, entry 1, ESI†). Most striking, the reaction can be effectively performed with a catalyst loading of 0.025 mol% still providing the coupled product in 88% yield (Fig. 4, and Table S2, Entry 2, ESI†). The optimal temperature was found to be 90 °C while lower temperature resulted in lower yield (Table S2, entries 3 and 4, ESI†). Further we examined various conditions with respect to catalyst, bases, and solvents to understand and

improve the catalytic performance of Cu₂₉NC on the cross-coupling reactions (Table S2, entries 5–12, ESI†). Solvent optimizations indicate that CH₃CN provided more yield in the case of a C–O coupling reaction while DMSO is better for other cross-couplings (C–N and C–S bond formations, see details in Table S3 and S4, ESI†). In order to better understand the catalyst efficacy, optimization studies were performed in the presence of two different electrophiles (*p*-bromobenzonitrile and *p*-bromoanisole) with *p*-cresol as the nucleophile under standard reaction (Fig. 4). As direct comparison, CuCl was investigated as a catalyst instead of Cu₂₉NC (Fig. 4), leading to lower efficiency (~22% yield), which is in line with the previous work.^{17,18}

Control experiments demonstrated that the absence of the Cu₂₉NC catalyst or a base resulted in no reaction or trace amounts observed (Table S2, entries 13 and 17, ESI†). Notably, the current Cu₂₉NC catalyst can be supported on different surfaces (Celite S, Celite 545, alumina (γ), CeO₂, and carbon powder) and tested for the C–O coupling reaction. These findings indicate that 0.025 mol% of Cu₂₉-Celite S is an effective C–O cross-coupling catalyst, with similar efficiencies to the unsupported cluster (Fig. 4 and details in ESI†), while also providing higher recyclability than other supports. Furthermore, Cu-complexes, namely Cu(I) S^tBu-PPh₃ and Cu(I) S^tBu (precursors for the preparation of Cu₂₉NC), were used as catalysts. However, the desired C–O coupling products (3 and 4) were obtained in lower yields with both, activated electrophiles (<42% yield) and unactivated electrophiles (<22% yield) compared to Cu₂₉NC (which yields 88%) (See, Fig. 4). Previously, we used Cu₆₁NC and Cu₂₈NC for photocatalytic C(sp²)[–] Nhet Ullmann–Goldberg coupling⁵⁴ and Sonogashira C–C cross-coupling reaction,⁵² respectively. In this regard, we performed control experiments with Cu₆₁NC and Cu₂₈NC as catalysts instead of Cu₂₉NC for the current C–O cross-coupling reactions, however, they produced low yields, 58% and 63%, respectively (Table S2, entries 8 and 9, ESI†). Thus, we hypothesize that the differently oriented chloride rich motif structures of Cu₂₉NC plays a key role in this reaction's efficiency.

Recyclable Cu₂₉NC catalyst development

In order to convert the Cu₂₉NC nanocluster into a heterogeneous recyclable catalyst, we aimed to attach the catalyst to a support. Thus, we prepared five different supported clusters (Cu₂₉-Celite S, Cu₂₉-Celite 545, Cu₂₉-alumina (γ), Cu₂₉-CeO₂, and Cu₂₉-carbon powder) and compared the three-reaction parameters, catalyst loading, performance, and leaching, to find the best heterogeneous catalyst. Details of their synthesis are described in the experimental section of the ESI.† The catalyst systems Cu₂₉-Celite S, Cu₂₉-CeO₂, and Cu₂₉-alumina (γ) showed better loading and performance than the remaining two systems (Fig. S12 and S13, ESI†). Interestingly, Cu₂₉-CeO₂ and Cu₂₉-alumina (γ) showed a higher amount of leaching after the 1st cycle, whereas a negligible amount of leaching was observed for Cu₂₉-Celite S (Fig. S14, ESI†). Thus, recyclability was further studied with the Cu₂₉-Celite S system. The diffuse reflectance optical spectrum of the pure Cu₂₉ cluster showed

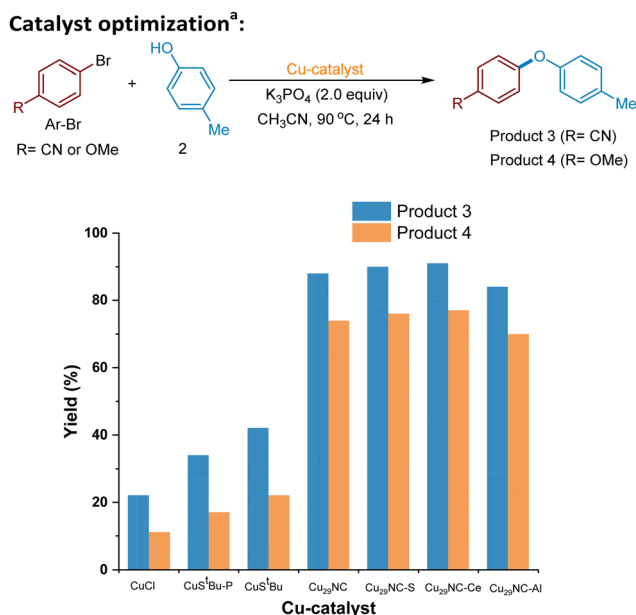


Fig. 4 Catalyst optimization. ^aConditions: Ar–Br (0.3 mmol), 2 (0.375 mmol), Cu-catalyst used such as 5 mol% of CuCl or Cu^stBu-PPh₃, Cu^stBu or 0.025 mol% of Cu₂₉NC or Cu₂₉-Celite S or Cu₂₉NC-CeO₂ or Cu₂₉NC-Al₂O₃, K₃PO₄ (2.0 eq.), and acetonitrile (CH₃CN) (2 mL). The mixture was stirred at 90 °C for 24 h. Yield refers to GC yield using 1,3,5-trimethylbenzene (mesitylene) as the internal standard.



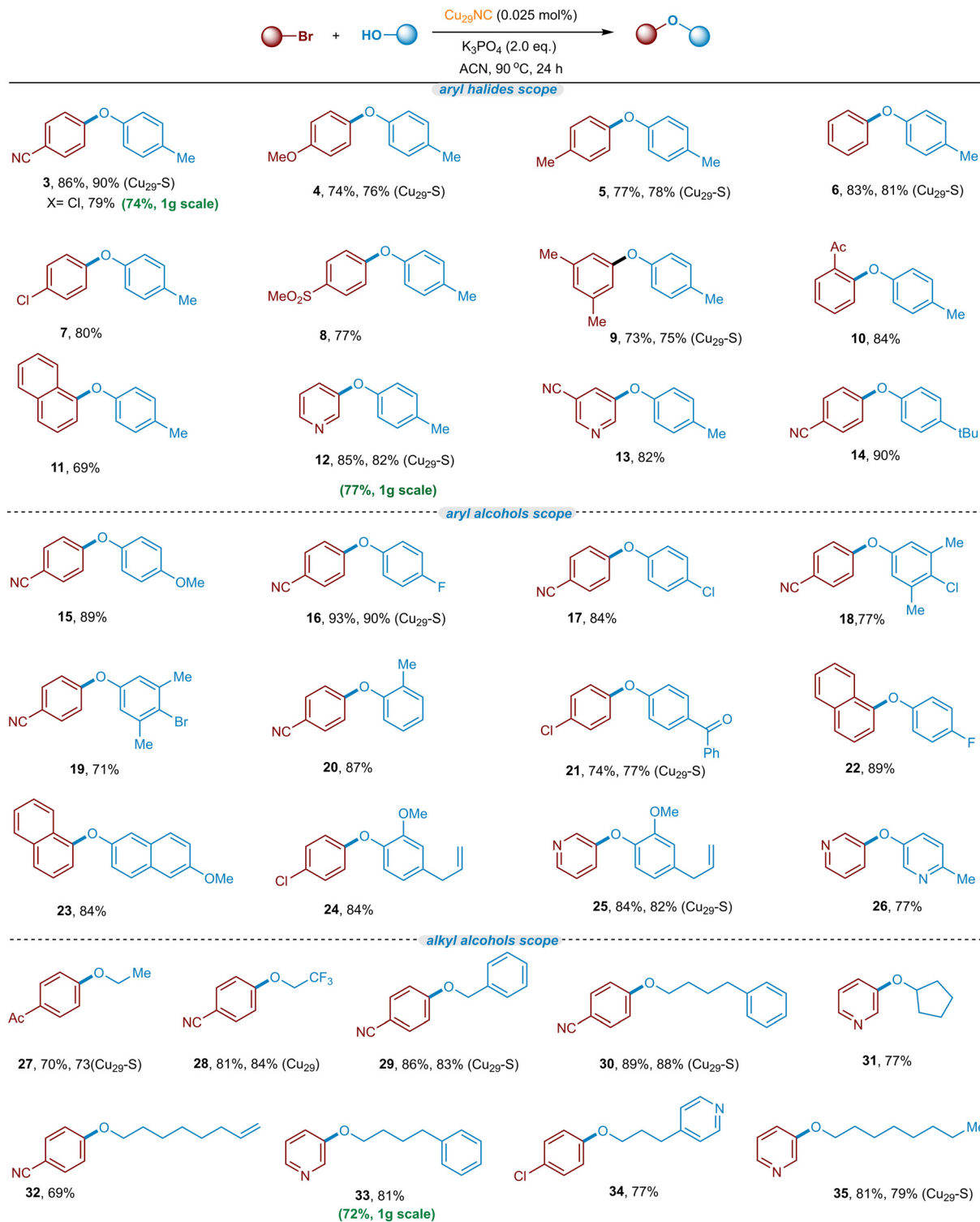


Fig. 6 Substrate scope of aryl halides and alcohols. Standard reaction conditions. Yield of isolated product after purification by column chromatography on a silica gel. (Cu₂₉-S) indicates heterogeneous Cu₂₉-Celite S.

the oxidative addition of Ar-X (X = Br, Cl) is operated by a concerted mechanism instead of a single electron transfer (SET). To further discern between concerted oxidative addition and SET pathways we carried out competition experiments. For example, the reaction with a 1 : 1 mixture of 4-chlorobenzonitrile (**1-Cl**) and

1-bromonaphthalene (**39**) with *p*-cresol as nucleophile, under standard conditions provides a product ratio of 1 : 14.2 (Scheme S5a, ESI[†]). Despite its lower reduction potential of **1-Cl**, **39** reacts faster, which can be related to the weaker C–Br bond compared to C–Cl. Consistently, a 1 : 1 mixture of **1-Cl** and 4-iodoanisole (**40**)



leads to a product ratio of 1:12.75 (Scheme S5b, ESI[†]). Overall, these results indicate that conventional two-electron oxidative addition is operative instead of a radical pathway *via* SET.^{54,79}

Electronic structure modeling of all possible intermediates along the reaction pathway were performed using a DFT approach^{80,81} (refer to ESI[†] for computational methods). In the DFT study we selected two different electrophiles, 4-bromoanisole and 4-chloroanisole, combined with the nucleophilic partner *p*-cresol. We started by identifying the most active site and elucidating an ensemble effect, which is the involvement of more than one Cu atom in Cu₂₉NC. To achieve this goal, we have relied on the thermodynamic feasibility of the first step, which is (Cu)₂₉-OAr formation *via* deprotonation by K₃PO₄. Different (Cu)₂₉-OAr intermediates were modeled (Fig. 7), by considering all the structurally different surface Cu-atoms on motifs 1–3 (Fig. 2). In addition to nine intermediates showing the nucleophile –OAr interacting with one single Cu atom (structures A₁–A₆ and A₈–A₁₀ in Fig. 7), we also identified one intermediate with the –OAr fragment bridging two adjacent Cu atoms, one of which is terminal (structure A₇ in Fig. 7). Intermediate A₇ is identified as the most stable one, suggesting for an ensemble effect favoring the initial activation of Cu₂₉NC. Other attempts to locate low energy structures with the –OAr fragment bridging two adjacent Cu atoms failed. Overall, the higher stability of structures A₄–A₇ indicate that motif 2 has more active Cu atoms compared to motifs 1 and 3.

All the intermediates along the reaction pathway and their relative energies are displayed in Fig. 8 involving 4-bromoanisole, and in Fig. S17 (refer to ESI[†]) for chloro analogue. As discussed above, the reaction starts with formation of the Cu–Nu bond in the presence of a strong base, K₃PO₄, which is exergonic by 138.1 kcal mol^{–1}. The resulting intermediate A₇ undergoes oxidative addition of 4-bromoanisole, since the alternative SET step is endergonic by 104.7 kcal mol^{–1} and can thus be excluded (Fig. S18, ESI[†]), consistently with the experimental evidence.

Within the conventional 2e oxidative addition scheme, two possible pathways (green vs. red paths in Fig. 8 were considered depending on the mechanism of Ar–Br activation. The first we considered involves a bimetallic mode of activation, with the Ar and Br moieties bound to two vicinal Cu atoms (green line

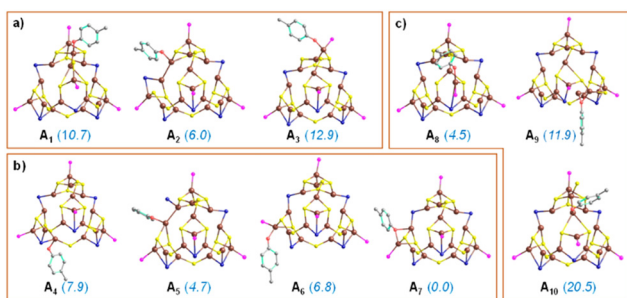


Fig. 7 DFT optimized structures and relative energies (in kcal mol^{–1}) of (Cu)₂₉-OAr complexes varying the active Cu-atom in three different regions: (a) motif 1, (b) motif 2, and (c) motif 3. Only surface Cu atoms are projected, and H atoms are omitted for clarity. The energy values are at the PBE-D3 level of theory using implicit solvation model in acetonitrile.

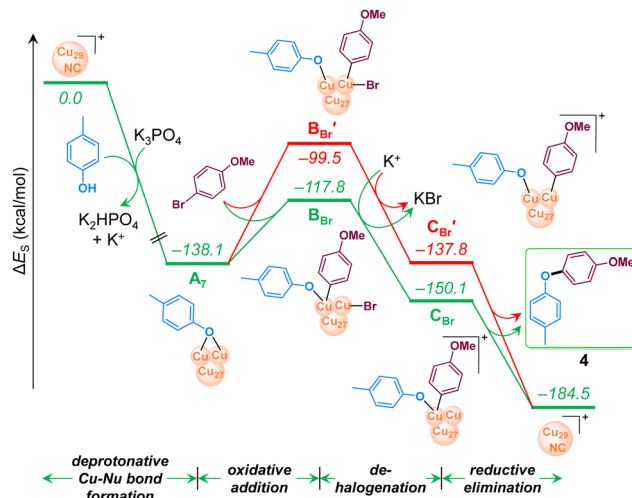
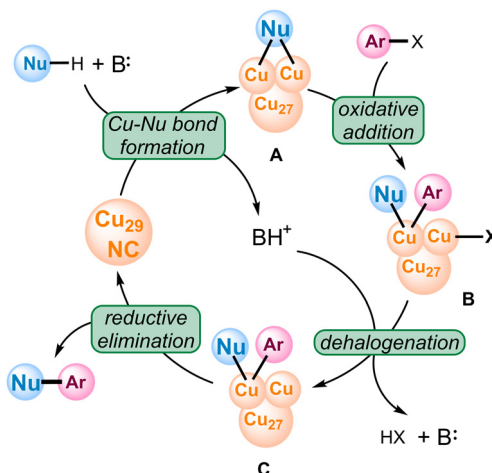


Fig. 8 Computed energy profile of Cu₂₉-NC catalyzed C–O coupling reaction of *p*-cresol using 4-bromoanisole. For energy convention, refer to Fig. 7.

in Fig. 8), is endergonic by 20.3 kcal mol^{–1} and leads to intermediate B_{Br}. The next step, debromination from B_{Br} results in the cationic intermediate C_{Br} with an energy gain of 32.8 kcal mol^{–1}. Finally, highly exergonic reductive elimination from C_{Br} results in the desired product and regenerates the starting Cu₂₉NC which is ready to start another catalytic cycle.

The second pathway we considered involves a standard monometallic oxidative addition of Ar–Br at a single Cu-atom (red line in Fig. 8), leading to the intermediate B_{Br}' which is 18.3 kcal mol^{–1} more unstable than the bimetallic intermediate B_{Br}. Consistently, the following debrominated intermediate, C_{Br}', is higher in energy than C_{Br} by 12.3 kcal mol^{–1}. Overall, the above results indicate that the pathway with bimetallic oxidative addition (green line) is more viable than the corresponding monometallic one (red line). Considering the initial reaction of Cu₂₉NC with the HO–Ar nucleophile, also favored by the presence of two nearby Cu atoms, our calculations indicate the role of an ensemble effect in favoring the whole reaction



Scheme 1 Proposed catalytic cycle.



pathway. Consistently, the computed energy profile for 4-chloroanisole (Fig. S17 in ESI†) resembles that of 4-bromoanisole (Fig. 8). To further acquire more insight into the kinetics involved, a linear one-dimensional scan analysis of the potential energy surface (PES) was conducted on the reaction rate-limiting step, oxidative addition of ArBr to A_7 (Fig. S19 in ESI†). By creating a series of “images” along the bond (C–Br) breaking during the reaction with a specific increment of the distance between the C

and Br with all atoms relaxed, an energy profile was described from which the energy barrier was predicted to be lower towards the formation of B_{Br} compared to that of B_{Br}' . The nudged elastic band and dimer methods were tested and deemed unfeasible due to the large size of the system.

Finally, based on our control experiments and computational results, we propose the catalytic cycle of the $Cu_{29}NC$ catalyzed C-heteroatom coupling reaction, shown in Scheme 1.

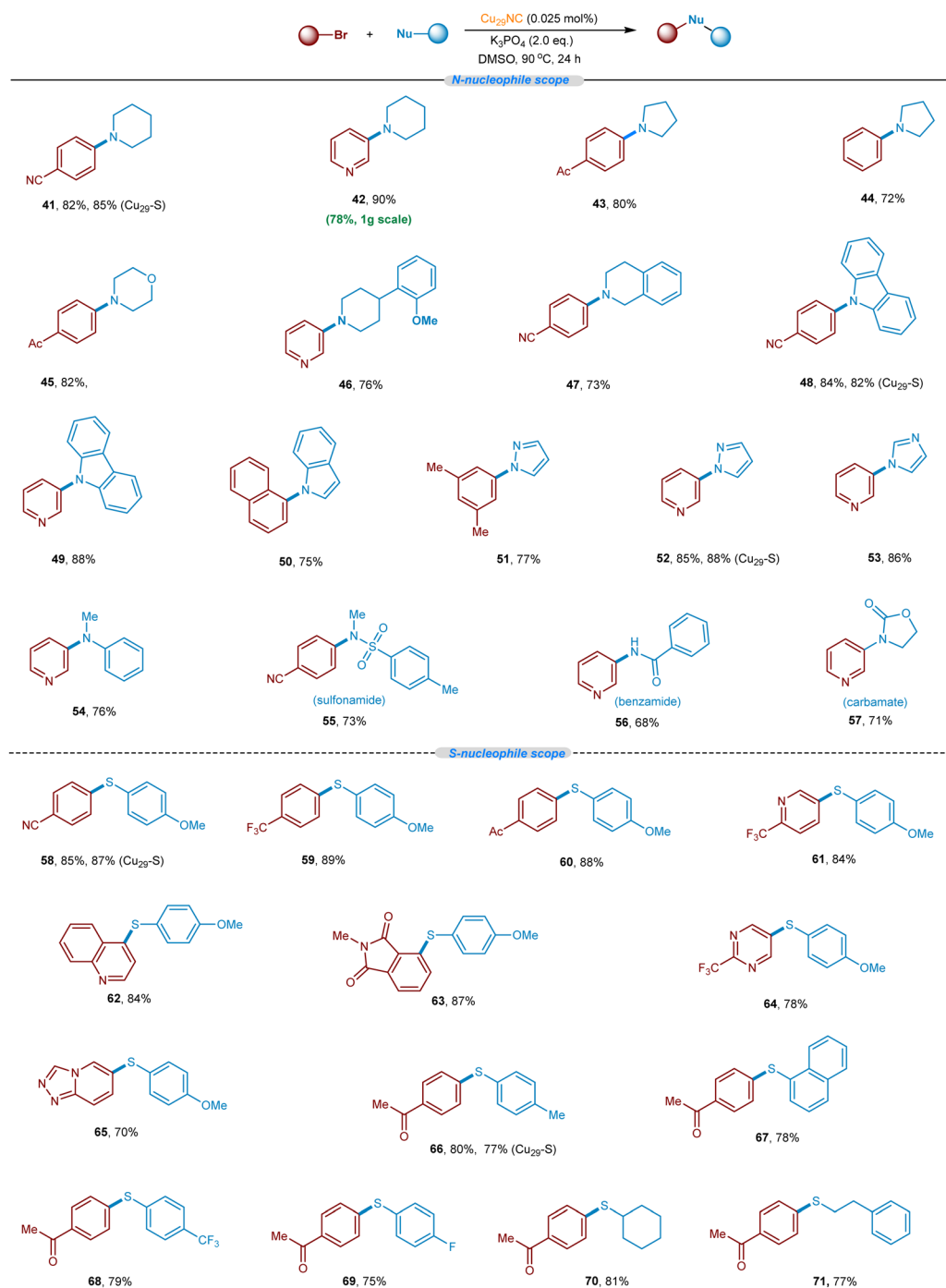


Fig. 9 Substrate scope of N-nucleophiles and S-nucleophiles with aryl halides. Standard reaction conditions. Yield of isolated product after purification by column chromatography on a silica gel. (Cu_{29} -S) indicates heterogeneous Cu_{29} -Celite S.



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