

FULL PAPER

Isocyanide Cu(I) complexes with unexpected μ_2 -bridging pseudohalides: Synthesis, characterization and catalytic activity towards CuAAC

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Three neutral Cu(I) complexes bearing 2,6-dimethylphenyl isocyanide (CNXyl) and different triatomic pseudohalogens (SCN⁻, OCN⁻ and N₃⁻) as ligands were efficiently synthesized and characterized. The solid-state structures were unambiguously determined through single-crystal X-ray diffraction, revealing unexpected bridging coordination modes in the case of OCN⁻ and N₃⁻. All the complexes were tested for azide-alkyne cycloaddition (CuAAC), showing interesting catalytic activity towards the formation of 1,4-disubstituted-1,2,3-triazoles for the cyanato and the azido Cu(I) complexes. Both species afforded yields above 90% with 0.5 mol% of catalyst at 50°C for 24 h. Several alkynes and azides were tested using the more active azido Cu(I) complex, affording the corresponding triazoles in high yields. The azido Cu(I) complex also induced the intramolecular CuAAC in the presence of dimethyl acetylenedicarboxylate and benzyl bromide/phenylacetylene.

KEYWORDS

azido, copper(I), CuAAC, isocyanide, pseudohalides

1 | INTRODUCTION

Isocyanides (C≡N–R) are often described as chameleonic ligands due to their electronic properties, which significantly vary depending on the metal centre they are coordinated to.^{1–4} Indeed, the activation of these species offers some advantages over the classic metal carbonyls. As a comparison with its isoelectronic counterpart CO, CNR exhibits stronger σ -donor and weaker π -acceptor abilities together with the possibility of modifying steric effects, metal–carbon bond strengths, chirality and even hydro-lipophilicity by modulation of the R groups.^{5–9} All these aspects make them suitable candidates to be applied for a wide variety of metal-mediated transformations,¹⁰ including C–H bond functionalization

via CNR insertion,^{11–14} N-heterocycle or N-acyclic diamino carbene formation¹² and photocatalysis.^{15,16}

To the best of our knowledge, we recently reported the first example of a trigonal homoleptic isocyanide Cu(I) complex that showed catalytic activity for copper azide-alkyne cycloaddition (CuAAC) in neat conditions.¹⁷ CuAAC is widely recognised as one of the brightest examples of *click* chemistry.^{18,19} This sustainable approach allows the synthesis of 1,4-disubstituted-1,2,3-triazoles in the presence of Cu(II) precursors and reducing agents, which generate in situ the active Cu(I) species.^{20–22} The direct use of Cu(I) catalysts enables the CuAAC reaction without the utilization of reductants or surfactants,²³ minimizing the load of reagents and the risk of side reactions. In this context,

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using suitable isocyanides can accomplish two-fold goals: (i) the stabilization of the Cu(I) metal centre, avoiding the extra-addition of bulky ligands or phosphines; and (ii) the modulation of the properties of the corresponding complexes through small modifications on the R groups.

Several trigonal planar and tetrahedral homoleptic derivatives having general formulae $[\text{Cu}(\text{CNR})_n]^+$ [$n = 3$ or 4 ; R = 2-methoxyisobutyl, *tert*-butyl, 2-(carbomethoxy)-2-methylethyl],^{24–26} and heteroleptic complexes with different coordination motifs and in combination with halides, phosphines, N- or other C-donor ligands were isolated.^{27–31} For instance, Fox et al. described a stable three-coordinated *m*-terphenyl based $[\text{CuCl}(\text{CNAr}^{\text{Mes}2})_2]$ (Mes = 2,4,6-Me₃C₆H₂) that can form $[\text{Cu}(\mu\text{-Cl})(\text{THF})(\text{CNAr}^{\text{Mes}2})_2]$ by adding a second equivalent of CuCl in THF solutions.⁵ However, only the heteroleptic chain polymer $[\text{CuCl}(\text{CNR})]_n$ (CNR = 2,4-dimethoxyphenyl isocyanide) described by Liu and Reiser was efficiently used as heterogeneous catalyst for CuAAC.³² In all the other cases, no evidence of catalytic activity for CuAAC was mentioned.

Despite being much less investigated, pseudohalides such as SCN[−], OCN[−] and N₃[−] exhibit similar chemical behaviour to halides but can provide significant electronic differences and peculiar reactivity.^{33,34} Therefore, given our interest in the synthesis and reactivity of isocyanide Cu(I) complexes¹⁷ and their proven non-innocent role in catalysis,¹⁰ we deemed it interesting to study their effect in combination with 2,6-dimethylphenyl isocyanide (CNXyl).

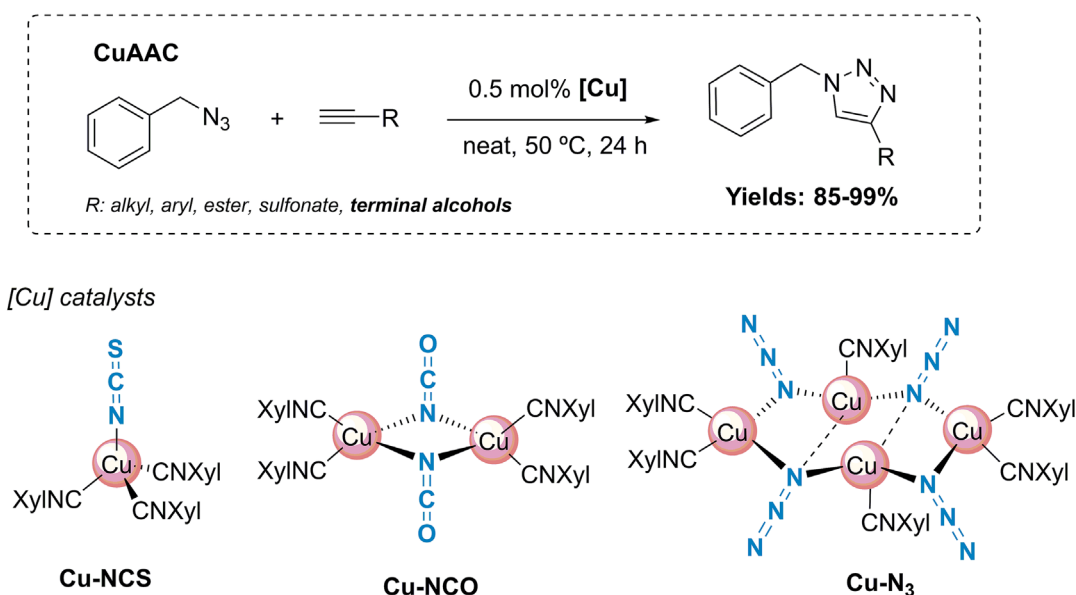
Herein, we report the synthesis and characterization of a family of neutral isocyanide Cu(I) complexes having SCN[−], OCN[−] and N₃[−] as pseudohalide ligands (see Scheme 1). To the best of our knowledge, the μ_2 -bridging behaviour of OCN[−] and N₃[−] groups in Cu(I) complexes has never been described before. These derivatives also exhibited promising results for the CuAAC. The reactivity of the azido Cu(I) complex was tested in combination with stoichiometric amounts of dimethyl acetylenedicarboxylate (DMAD) and benzyl bromide/phenylacetylene (BzBr/PA), affording the corresponding product of intramolecular azide-alkyne cycloaddition.

2 | EXPERIMENTAL

2.1 | Materials and methods

$[\text{Cu}(\text{NCCH}_3)_4]\text{BF}_4$ was obtained from Cu₂O following a reported synthesis.³⁵ Benzyl and 4-methylbenzyl azides,³⁶ 2-azidoethylamine³⁷ and ethyl 5-azide valerate³⁸ were synthesized following literature procedures. 4-(Methylsulfonyl)but-1-yne was synthesized following the method reported by Takizawa et al.³⁹ All the other reagents and solvents were purchased from Merck and used as received unless noted. *Safety disclaimer:* azido Cu(I) complexes can be explosives and should be handled carefully!

Infrared (IR) spectra in dichloromethane and KBr matrix were, respectively, recorded in the 4000–400 cm^{−1} range with Frontier PerkinElmer Spectrum RX I FT-IR



SCHEME 1 Cu(I) complexes tested in this work for the copper azide-alkyne cycloaddition (CuAAC) of 1,4-disubstituted-1,2,3-triazoles. [Cu] = **Cu-NCS**, **Cu-NCO** and **Cu-N₃** (CNXyl = 2,6-dimethylphenyl isocyanide).

and PerkinElmer Spectrum One spectrophotometer instruments. Monodimensional nuclear magnetic resonance (NMR) spectra in CDCl_3 or $\text{DMSO}-d_6$ were collected employing Bruker Avance 300 and 400 instruments operating, respectively, at 300.13 and 400.13 MHz of ^1H resonances. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra refer to the partially non-deuterated fraction of the solvent, itself quoted as tetramethylsilane. Gas-liquid chromatography (GLC) analyses were performed on an Agilent 6850 chromatograph.

2.2 | Synthesis and characterization of the complexes

2.2.1 | $[\text{Cu}(\text{NCS})(\text{CNXyl})_3]$, (Cu-NCS)

Over a suspension of CuSCN (0.041 g, 0.3 mmol) in 15 mL of dry MeOH, CNXyl was added (0.131 g, 1.0 mmol) under stirring. After 30 min, the reaction mixture was concentrated and precipitated with hexane. The microcrystalline white solid was dried in vacuo. Yield: 0.165 g, 95%. Crystals suitable for X-ray diffraction (XRD) were collected from MeOH/diethyl ether solutions at room temperature. IR (cm^{-1}): 3060–2860 (w, ν_{CH}), 2148 (vs, $\nu_{\text{C}\equiv\text{N}}$), 2087 (s, ν_{SCN}), 1490–1440 (m, $\nu_{\text{C}=\text{C}}$). Anal. Calcd. for $\text{C}_{28}\text{H}_{27}\text{CuN}_4\text{S}$: C, 65.28; H, 5.28; N, 10.88. Found C 65.43, H 5.17, and N 10.70. ^1H NMR (400 MHz, CDCl_3) δ 7.25 (t, $^3J_{\text{HH}} = 7.3$ Hz, 3H, H^4), 7.13 (d, $^3J_{\text{HH}} = 7.3$ Hz, 6H, $\text{H}^{3,5}$), 2.49 (s, 18H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 152.98 $\text{N}\equiv\text{C}$, 135.45 $\text{C}^{2,6}$, 129.99 NCS , 129.46 C^4 , 127.99 $\text{C}^{3,5}$, 126.23 C^1 , 18.66 C^{CH_3} .

2.2.2 | $[\text{Cu}(\mu\text{-NCO})(\text{CNXyl})_2]_2$, (Cu-NCO)

Over a solution of $[\text{Cu}(\text{NCCH}_3)_4]\text{BF}_4$ (0.157 g, 0.5 mmol) in 15 mL of dry MeOH, CNXyl (0.131 g, 1.0 mmol) and NaNCO (0.033 g, 0.5 mmol) were added under stirring. After 30 min, the solvent was evaporated and then dichloromethane (DCM) was added. The solution was filtered over celite, concentrated and precipitated with hexane. The yellow microcrystalline solid was dried in vacuo. Yield: 0.260 g, 96%. Crystals suitable for XRD were collected from MeOH/diethyl ether solutions at room temperature. IR (cm^{-1}): 3070–2860 (w, ν_{CH}), 2163 (vs, $\nu_{\text{C}\equiv\text{N}}$), 2151 (vs, $\nu_{\text{C}\equiv\text{N}}$), 2212 (vs, ν_{OCN}), 1475–1450 (m, $\nu_{\text{C}=\text{C}}$). Anal. Calcd. for $\text{C}_{38}\text{H}_{36}\text{Cu}_2\text{N}_6\text{O}_2$: C, 62.03; H, 4.93; N, 11.42. Found: C, 62.21; H, 4.73; N, 11.29. ^1H NMR (400 MHz, CDCl_3) δ 7.23 (t, $^3J_{\text{HH}} = 7.7$ Hz, 2H, $\text{H}^{4,\text{Xyl}}$), 7.12 (m, 4H, $\text{H}^{3,5,\text{Xyl}}$), 2.47 (s, 12H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 135.61 $\text{C}^{2,6}$, 129.63 C^4 , 128.13 $\text{C}^{3,5}$, 126.35 C^1 , 19.02 C^{CH_3} .

2.2.3 | $[\text{Cu}_2(\mu\text{-N}_3)_2(\text{CNXyl})_3]_2$, (Cu-N₃)

Over a solution of $[\text{Cu}(\text{NCCH}_3)_4]\text{BF}_4$ (0.157 g, 0.5 mmol) in 15 mL of dry MeOH, CNXyl (0.197 g, 1.5 mmol) and NaN_3 (0.033 g, 0.5 mmol) were added under stirring. After 60 min, the pale pink suspension was filtered over a fritted funnel, washed and dried in vacuo. Yield: 0.130 g, 86%. Crystals suitable for XRD were collected from MeOH/diethyl ether solutions at room temperature. IR (cm^{-1}): 3070–2865 (w, ν_{CH}), 2137 (vs, $\nu_{\text{C}\equiv\text{N}}$), 2039 (vs, ν_{N_3}), 1470–1440 (m, $\nu_{\text{C}=\text{C}}$). Anal. Calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_9\text{Cu}_2$: C, 53.63; H, 4.50; N, 20.85. Found: C, 53.29; H, 4.73; N, 20.68. ^1H NMR (400 MHz, CDCl_3) δ 7.24 (t, $^3J_{\text{HH}} = 7.8$ Hz, 3H, $\text{H}^{4,\text{Xyl}}$), 7.11 (m, 6H, $\text{H}^{3,5,\text{Xyl}}$), 2.48 (s, 18H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 135.46 $\text{C}^{2,6}$, 129.46 C^4 , 127.97 $\text{C}^{3,5}$, 126.21 C^1 , 18.95 C^{CH_3} .

2.3 | X-ray structure determination

XRD data were collected using an Oxford Diffraction Supernova diffractometer, equipped with an Atlas CCD area detector and a four-circle kappa goniometer. For the data collection, a Mo source with multilayer optics was used. Data integration, scaling and empirical absorption correction were carried out using the CrysAlis Program package.⁴⁰ The structures were solved using direct methods and refined by full-matrix least-squares against F^2 with SHELX^{41,42} under OLEX2.⁴³ The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed at idealized positions and refined using the riding model. Full-matrix least-squares refinements were carried out by minimizing $\sum w(F_o^2 - F_c^2)^2$ with the SHELXL weighting scheme and stopping at shift/err < 0.001. The final residual electron density maps showed no remarkable features. Graphics were made with OLEX2 and MERCURY.^{43–45} Crystal data, structural refinement and Cambridge Crystallographic Data Centre (CCDC) reference numbers are given in Table S1. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited in the CCDC as supplementary publication no. CCDC 2227034, 2227035, 2227036, 2227037, 2227038.

2.4 | Catalytic tests

The azide (1.0 mmol) and the alkyne (1.1 mmol) were added into a 10 mL vial closed with a screw cap. The **Cu-NCO** complex was added in 2 mL of MeOH, while in the case of the **CuN₃** complex, 4 mL of a 1:1 mixture of MeOH/DCM were used. Finally, complex **Cu-NCO** or **Cu-N₃** (0.05–5 mol%) were added, and the reaction was

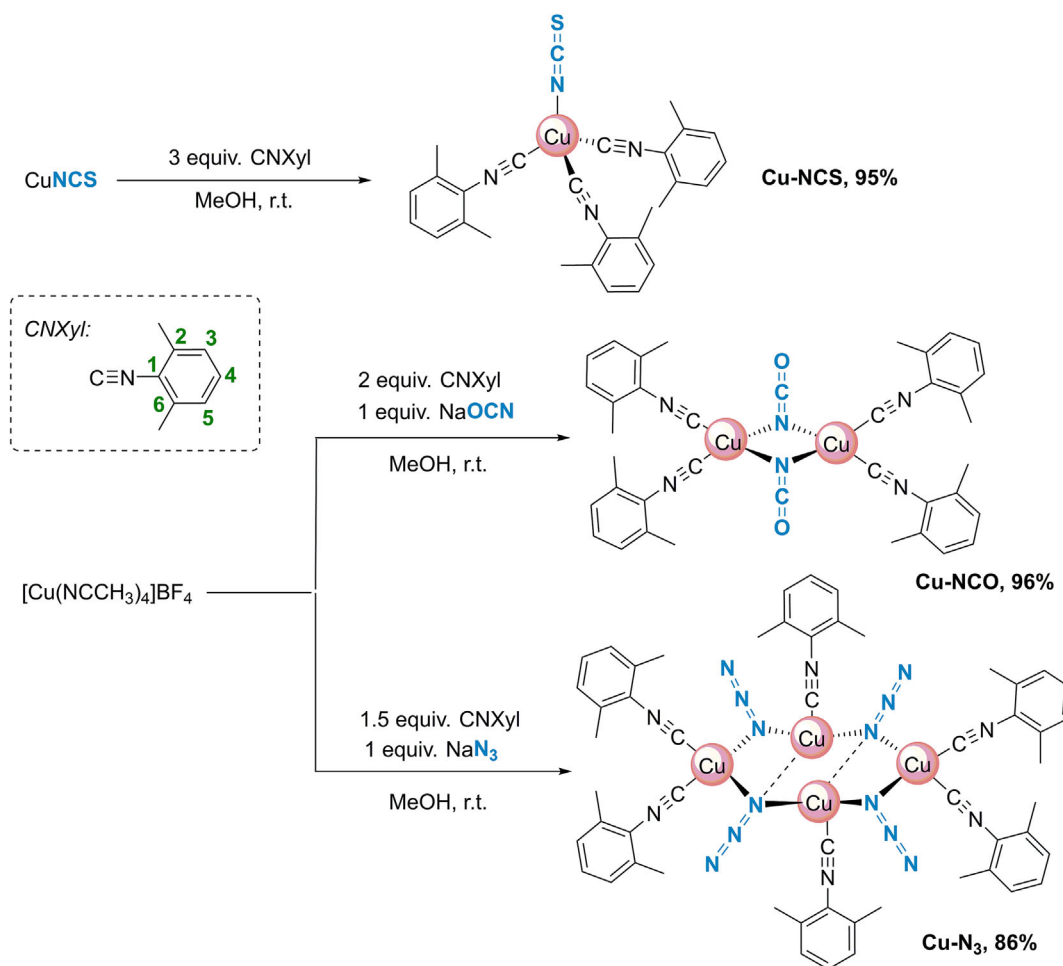
allowed to proceed at 50°C and monitored via thin-layer chromatography (TLC). After the total consumption of the starting azide (24 h), the solvent was evaporated under reduced pressure, the product was precipitated with hexane, collected by filtration and washed with hexane. When the corresponding 1,4-disubstituted-1,2,3-triazole was an oil, the reaction mixture was concentrated under vacuum, and the residue was finally purified on silica gel (hexane/ethyl acetate). Yields reported are an average of at least two experiments.

3 | RESULTS AND DISCUSSION

3.1 | Synthesis and characterization of the complexes

As previously reported by us, the reaction of $[\text{Cu}(\text{NCCH}_3)_4]\text{BF}_4$ with three equivalents of 2,6-dimethylphenyl isocyanide (CNXyl) in mild conditions produced the homoleptic trigonal planar complex $[\text{Cu}$

$(\text{CNXyl})_3]\text{BF}_4$.¹⁷ One equivalent of the appropriate pseudohalide sodium salt (NaN_3 , NaOCN or NaSCN) was added to three different MeOH solutions of $[\text{Cu}(\text{CNXyl})_3]\text{BF}_4$ to synthesise the tetracoordinated $\{\text{Cu}(\text{CNXyl})_3\}$ -pseudohalide complexes. However, only in the case of the **Cu-NCS** complex, the corresponding tetrahedral derivative was isolated, revealing to be air-stable and soluble in common organic solvents. On the contrary, the addition of a stoichiometric amount of NaOCN and NaN_3 to $[\text{Cu}(\text{CNXyl})_3]\text{BF}_4$ determined the isolation of the unexpected multinuclear species **Cu-NCO** and **Cu-N₃**. Further attempts towards the formation of different structures by varying the amounts of NaOCN and NaN_3 always led to **Cu-NCO** and **Cu-N₃**, which appear to be the most stable species. Accordingly, the synthesis of the two complexes was optimized by using the required stoichiometry (see Scheme 2 and Section 2), affording both compounds in excellent yields. $[\text{Cu}(\text{NCCH}_3)_4]\text{BF}_4$ was employed as a precursor because the use of azido and cyanato Cu(I) salts is compromised by their explosiveness and instability in common organic solvents.^{46,47}



SCHEME 2 Optimised synthesis of the Cu(I) isolated complexes.

The heteronuclear NMR spectra of these three products were almost superimposable to those reported for $[\text{Cu}(\text{CNXyl})_3]\text{BF}_4$ (see Figures S1–S12 for ^1H , ^{13}C , ^1H - ^{13}C $\{^1\text{H}\}$ HSQC and HMBC NMR original spectra).¹⁷ On the other hand, the FT-IR monitoring (see Figures S13–S15) showed a displacement of the CNXyl stretching bands ($\Delta\nu$) of 25, 40 and 14 cm^{-1} , respectively, for **Cu-NCS**, **Cu-NCO** and **Cu-N₃** from the free CNXyl, and the characteristic pseudohalide frequencies in the 2300–2000 cm^{-1} region (ν_{NCO} 2087, ν_{NCS} 2212 and ν_{N_3} 2055 cm^{-1}).⁴⁸ Free isocyanide ligand ($\nu_{\text{C}\equiv\text{N}}$ 2123 cm^{-1}) was also detected in the reactions, indicating some decomposition process or ligand rearrangement.

After the proper workups, suitable crystals were obtained and analysed by XRD (see Figures 1–3 and crystallographic data in the Supporting Information). Indeed, the exhaustive elucidation of each single crystal structure revealed the unexpected coordination motifs described in Scheme 1, which agreed with the FT-IR experimental discussion. Other minor Cu(I) species (less than 5%) containing SCN^- and NCO^- ligands were isolated from the bulks, and they were also studied by single crystal XRD (see Figures S16–S17 and Table S1).

The solid-state structure of **Cu-NCS** displayed in Figure 1 presents a tetracoordinated surrounding as reported for other $\{\text{Cu}(\text{CNR})_3\}$ -halide complexes,⁴⁹ with the SCN^- ligand occupying the apical position at 0.632 Å out from the plane. The SCN^- ligand remains linear, being characterized by a 179.22° N(4)-C(4)-S(1) angle.

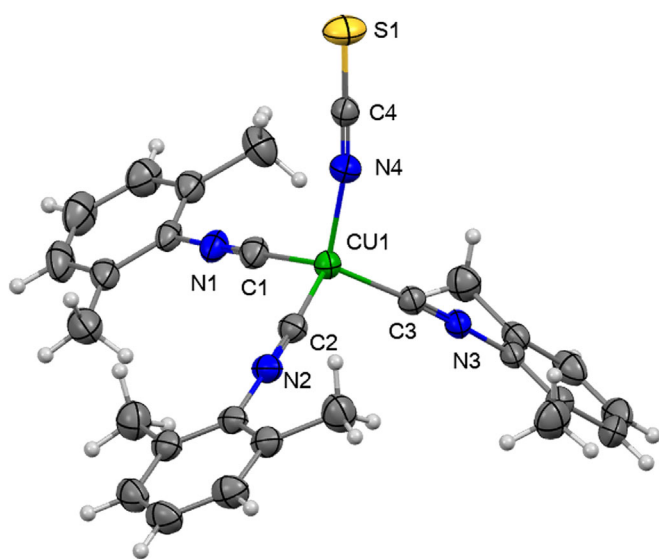


FIGURE 1 Perspective view of compound **Cu-NCS** showing the atom numbering. Selected bond distances (Å) and angles (°): Cu(1)-C(1), 1.938(3); Cu(1)-C(2), 1.931(2); Cu(1)-C(3), 1.934(2); Cu(1)-N(4), 1.982(2); C(1)-Cu(1)-C(2), 109.48(2); C(2)-Cu(1)-C(3), 113.60(1); C(3)-Cu(1)-N(4), 111.11(9); N(4)-Cu(1)-C(1), 106.80(1); N(4)-Cu(1)-C(2), 109.15(9).

Instead, the Cu(1)-N(4)-C(4) angle deviates significantly from linearity to 170.1(2)°. Quite surprisingly, the bond lengths Cu(1)-N(4) 1.982(2) and N(4)-C(4) 1.143(3) Å are significantly shorter than values observed for similar compounds.⁴⁸

The neutral structures of **Cu-NCO** and **Cu-N₃** show *end-on* (EO) pseudohalide bridges between Cu(I) atoms. As far as we know, these are the only two Cu(I) complexes reported where the pseudohalide is μ_2 -bridging to the metal centre. In all the other structures described in the literature, the pseudohalides are terminal and coordinated exclusively to one Cu(I).^{33,46,47,50–57} In particular, the geometry of **Cu-NCO** illustrated in Figure 2 shows each Cu(I) atom coordinated to two CNXyl ligands and one OCN^- group, which generates a centrosymmetric dimer by a long contact between the N atom and a nearby molecule with concerted unsymmetrical two nitrogen bridges (Cu(1)-N(3) of 2.071(2) and 2.122(2) Å). The angle N(3)-Cu(1)-N(3') of 92.31(9)° places both OCN^- groups in apical positions, displaced by 1.509 Å from the basal plane, which is delimited by the two tetrahedral copper ions and the isocyanide ligands.

Interestingly, the solid-state structure of **Cu-N₃** reported in Figure 3 exhibits two different copper coordination modes in a crown-like eight-membered cycle. Cu(1) is bonded to two CNXyl and two EO azido ligands through nitrogen bridges, whereas Cu(2) is linked to one isocyanide and two EO azido ligands. The latter completes the tetrahedral geometry through close contact with an N atom across the cycle with a Cu(2)-N(1') bond of 2.572(2) Å. The Cu-N bonds are slightly asymmetric, hence the azido ligand is slightly distorted from the linear geometry with angles, respectively, of 178.5(3) and 178.9(3)°.

3.2 | Catalytic tests

With the fully characterized complexes in hand, we deemed it interesting to evaluate their activity towards the CuAAC *click* reaction (see Table 1). The target reaction between benzyl azide and PA was carried out under different conditions to optimise the reaction parameters. In agreement with the reaction conditions generally adopted for the CuAAC,^{16,18,58,59} the three Cu(I) complexes were initially tested in the presence of a 5 mol% catalyst loading at room temperature in 2 mL of MeOH (**Cu-N₃** was insoluble in pure MeOH and required a 1:1 MeOH/DCM solution). After 6 h, only **Cu-NCO** and **Cu-N₃** showed catalytic activity, giving complete selectivity towards the 1-benzyl-4-phenyl-1*H*-1,2,3-triazole with yields of 64% and 88%, respectively

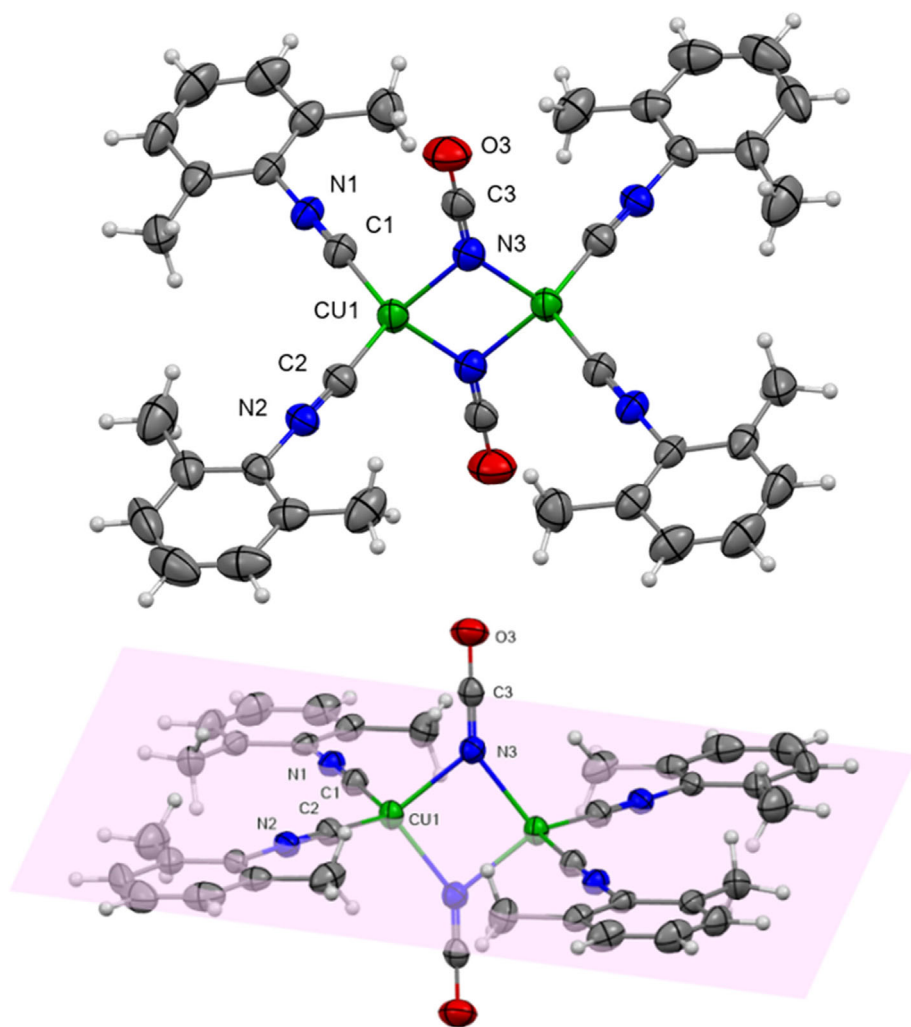


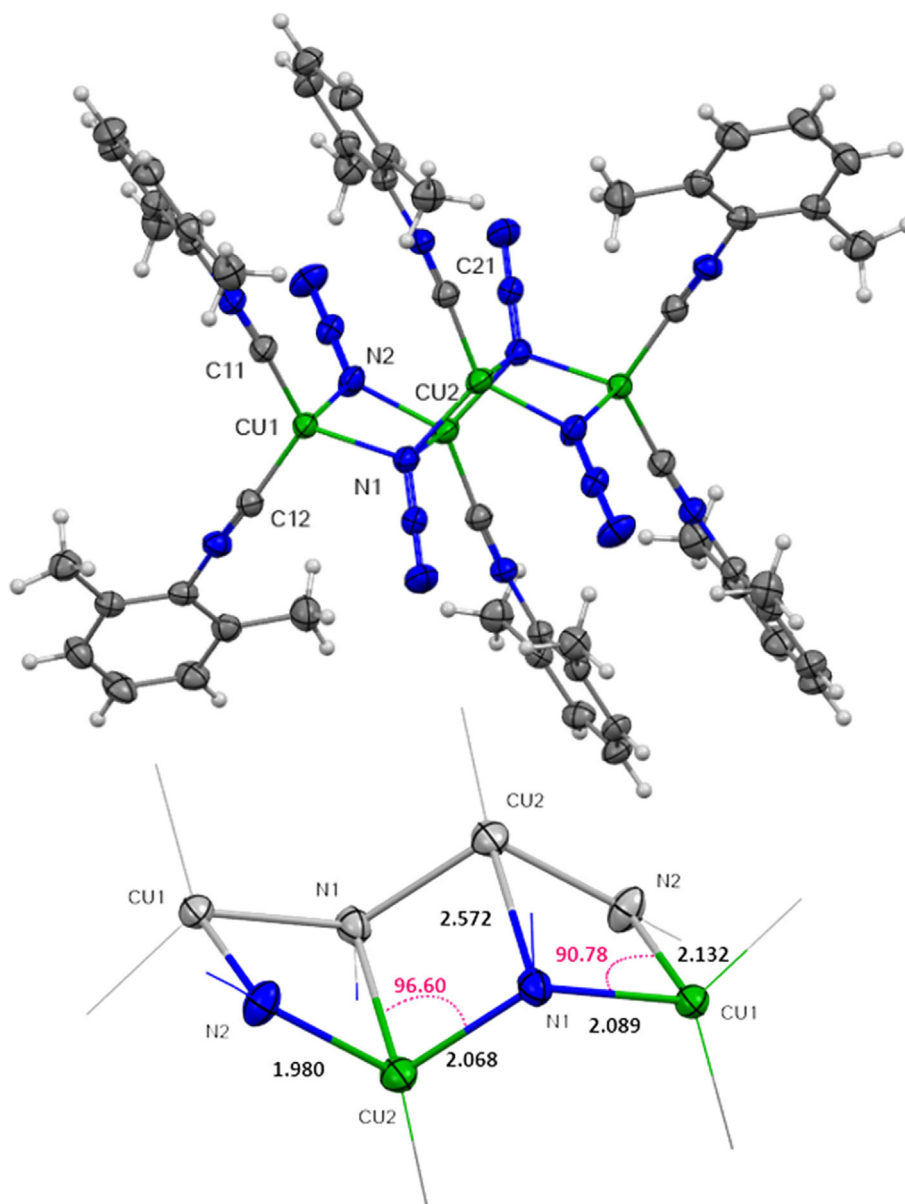
FIGURE 2 Above: X-ray structure of **Cu-NCO**. Selected bond distances (Å) and angles (°): Cu(1)-C(1) 1.909(3); Cu(1)-C(2) 1.895(3); Cu(1)-N(3) 2.071(2); Cu(1)-N(3') 2.122(2); C(1)-Cu(1)-C(2), 176.9(2); N(3)-Cu(1)-N(3') 92.31(9)°. Below: perspective of the dimeric complex with the basal plane delimited by the copper ions and the CNXyl ligands.

(Table 1, Entries 1–3). Consequently, further experiments only involved the use of **Cu-NCO** and **Cu-N₃** complexes. Aiming to investigate the potential of the synthesized complexes, we reduced the catalyst loading to 0.5 mol% and increased the reaction time to 24 h. At these conditions, 1-benzyl-4-phenyl-1*H*-1,2,3-triazole was obtained with yields under 70% (Table 1, Entries 4–5). It is worth mentioning that this represents a significant improvement if compared with the reports present in the literature concerning the use of CuCNR complexes for CuAAC.³² Nonetheless, to further explore the limit of the catalyst, the temperature was increased to 50°C, but the experiments carried out at 6 and 18 h afforded only moderate yields (Table 1, Entries 6–9), emphasizing the influence of the reaction time. After 24 h at 50°C, the corresponding triazole was obtained, respectively, in 97% yield for **Cu-NCO** and >99% for **Cu-N₃** (Table 1, Entries 10–11). Although a wide literature is available on Cu(I)-catalysed methods for the azide-alkyne cycloaddition, the presence of efficient protocols reporting such a low catalyst loading is rather limited.⁶⁰ Finally, a further

reduction of the catalyst loading to 0.05% and 0.1 mol% at 50°C and 24 h did not allow reaching complete conversions (Table 1, Entries 12–15). Thus, the optimized catalytic conditions selected were 0.5 mol% of **Cu-N₃**, 50°C and 24 h. To rule out the possibility that traces of the precursor [Cu(NCCH₃)₄]BF₄ could also be active towards the CuAAC, we tested the complex, but no conversion was observed in the optimized conditions used for **Cu-N₃**. Bearing in mind the principles of green chemistry, of which the CuAAC is one of the brightest examples, we tested some green solvents as alternatives, such as 2-methyltetrahydrofuran and cyclopentyl methyl ether. Unfortunately, the desired triazole was not detected in these conditions.

To verify the scope of the new catalyst, we attempted the synthesis of a small library of 1,4-disubstituted-1,2,3-triazoles by reacting a set of different alkynes and azides under optimized reaction conditions (see Scheme 3). ¹H and ¹³C{¹H} NMR data and spectra are collected in the Supporting Information for completeness (Table S2 and Figures S18–S46). The characterization

FIGURE 3 Perspective view of compound **Cu-N₃** showing the atom numbering. Selected bond distances (Å) and angles (°): Cu(1)-N(1), 2.089(2); Cu(1)-N(2), 2.132(2); Cu(2)-N(1), 2.068(2); Cu(2)-N(2), 1.980(2); Cu(1)-Cu(2), 3.146; N(1)-Cu(1)-N(2), 90.78(2); N(1)-Cu(2)-N(2), 96.70(2).



data is in agreement with the data reported in the literature for the same compounds obtained with different methods.^{17,61–69} General quantitative yields were obtained in these conditions with the presence of hindered groups, both aromatic and aliphatic alkynes (see, for instance, **T1–T4**; **T5–T8**; **T11**). On the other hand, the reaction of alkynes bearing terminal -OH groups is often limited by the interaction with the metal centre, as testified by the inactivity of the [Cu(CNXyl)₃]BF₄ complex previously tested by our group.¹⁷ Nevertheless, the **Cu-N₃** complex showed excellent activity when the reaction was run in the presence of propargylic alcohol, 2-methylbut-3-yn-2-ol and but-3-yn-1-ol (**T9**, **T10** and **T13**). Besides benzyl azide and *p*-methyl benzyl azide, ethyl 5-azidopentanoate was used as an aliphatic azide, affording the corresponding triazoles **T12** and **T13** in yields

higher than 95%. The catalytic system demonstrated good tolerance towards carbonyl groups, as stated by the high yields of **T14** and **T15**. On the other hand, the use of substrates containing -NH₂-SiMe₃ or S=O, such as 2-azidoethan-1-amine, trimethylsilylacetylene and but-3-yn-1-yl methanesulfonate, determined the rapid decomposition of the catalyst without the formation of any product. Attempts in the presence of internal alkynes, such as 1-phenyl-1-propyne, did not afford the expected compounds, neither by increasing the catalyst loading to 5% mol nor the temperature to 80°C.

No evidence of tetrazole formation from the cycloaddition between the azides and CNXyl was observed, suggesting that the catalytic active species are effectively **Cu-N₃** and **Cu-NCO** and no other eventual Cu(I) salt formed in solution. The different catalytic activity of

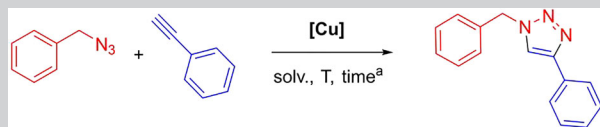
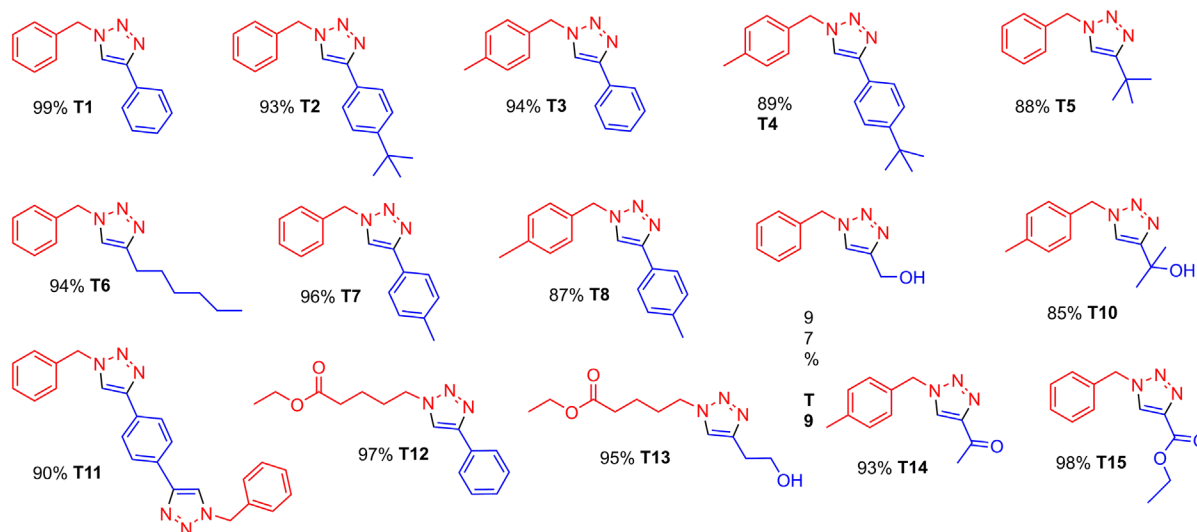


TABLE 1 Optimization of reaction conditions using Cu(I) neutral isocyanide complexes.

Entry ^a	[Cu] (mol% complex)	T (°C)	Time (h)	Yield (%) ^b
1	Cu-NCS, 5	20	6	0
2	Cu-NCO, 5	20	6	64
3	Cu-N ₃ , 5	20	6	88
4	Cu-NCO, 0.5	20	24	61
5	Cu-N ₃ , 0.5	20	24	68
6	Cu-NCO, 0.5	50	6	45
7	Cu-N ₃ , 0.5	50	6	77
8	Cu-NCO, 0.5	50	18	62
9	Cu-N ₃ , 0.5	50	18	86
10	Cu-NCO, 0.5	50	24	97
11	Cu-N ₃ , 0.5	50	24	>99
12	Cu-NCO, 0.05	50	24	5
13	Cu-N ₃ , 0.05	50	24	25
14	Cu-N ₃ , 0.1	50	24	43
15	Cu-NCO, 0.1	50	24	13

^aGeneral conditions: benzyl azide = 1.0 mmol; phenylacetylene = 1.1 mmol; 2 mL of MeOH for Cu-NCS and Cu-NCO; 4 mL 1:1 MeOH/DCM for Cu-N₃.

^bIsolated yield of final products.



SCHEME 3 Triazoles synthesized using Cu-N₃ as catalyst with isolated yields. Reaction conditions: azide = 1.0 mmol; alkyne = 1.1 mmol; cat. = 0.5 mol%; 50°C, 4 mL 1:1 MeOH/DCM, 24 h.

Cu-N₃ and Cu-NCO compared with Cu-NCS can be tentatively attributed to the different Cu-N bond distances. All the Cu(I) catalysts provide a tetrahedral coordination

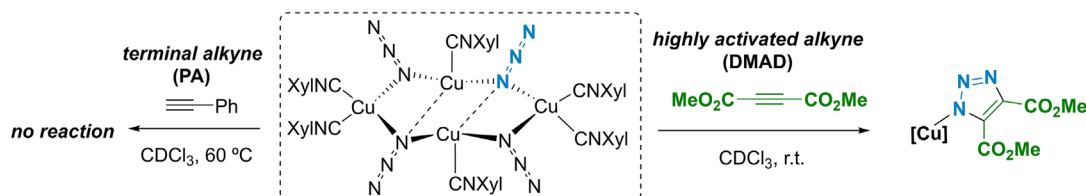
of the metal centre in the solid state, as it was confirmed by XRD. However, whereas Cu-NCS has a Cu-N distance of 1.982(2) Å, which is in the range of the Cu-N terminal

bonds, the nitrogen bridges in **Cu-NCO** and **Cu-N₃** complexes present elongated bonds equal to 2.071(2)/2.122(2) and 2.068(2)/2.089(2) Å, respectively. The increased lability in those bonds allows the coordination of the substrates and the evolution of the catalytic reaction in solution, similar to the previously reported [Cu(CNXyl)₃]BF₄.¹⁷ Thus, the Cu-N bond strength in **Cu-NCS** supports its inactivity for the CuAAC. In addition, based on DFT calculations and experimental outcomes, polynuclear

species enable concerted mechanisms in CuAAC because the azide and the alkyne are expected to coordinate two different but close Cu(I) atoms.^{70–75}

3.3 | Reactivity studies in complex **Cu-N₃**

As we mentioned before, few examples of azido Cu(I) complexes are reported in the literature, although



SCHEME 4 Stability studies of **Cu-N₃** complex with different alkyne compounds. Arbitrary N₃[−] ligand selected in the complex to show the plausible formation of the triazole final product. [Cu]: proposed metal moiety coordinated to formed triazole.

¹H NMR

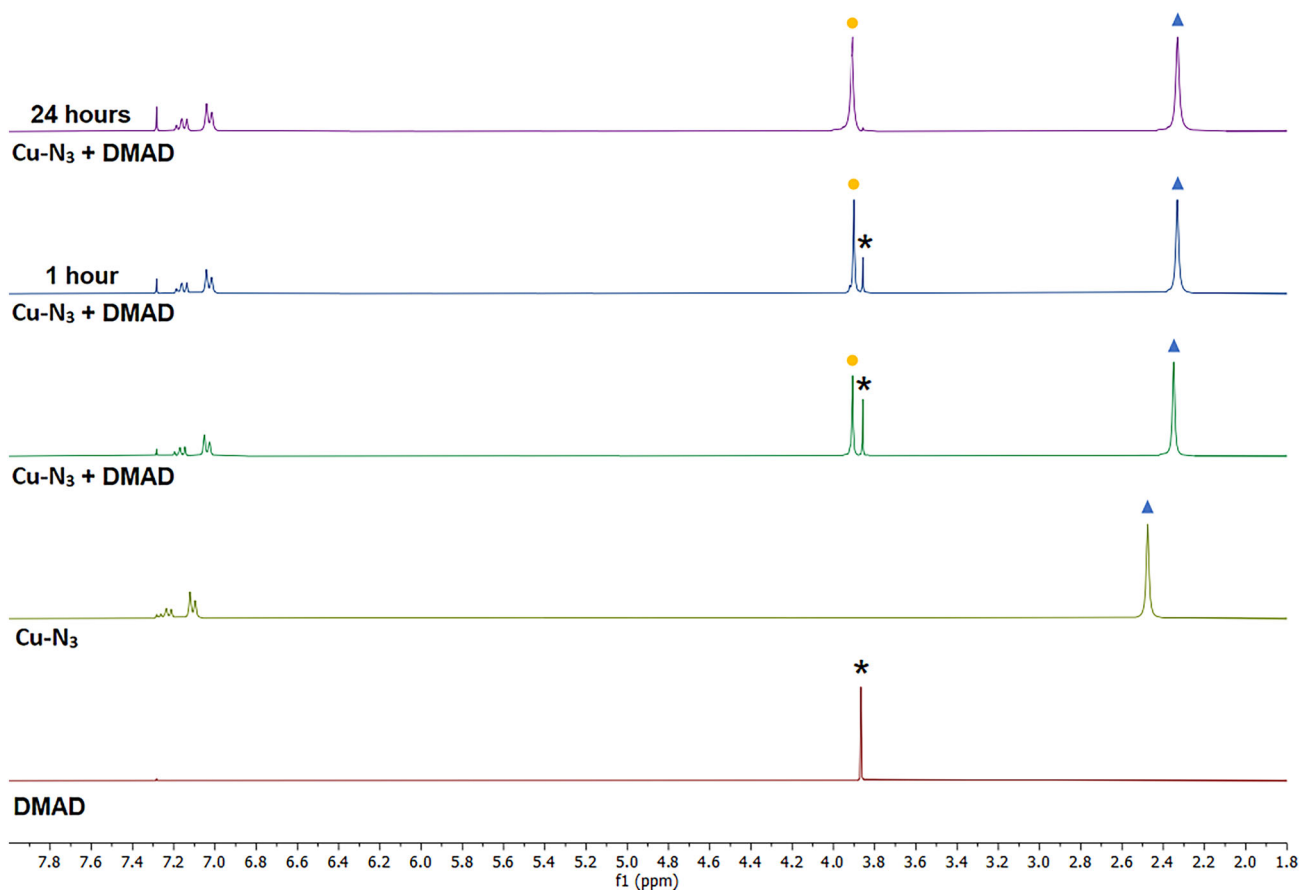


FIGURE 4 ¹H nuclear magnetic resonance (NMR) spectra of dimethyl acetylenedicarboxylate (DMAD), **Cu-N₃** and **Cu-N₃ + DMAD** (300 MHz, CDCl₃, 298 K). *Methyl groups in DMAD. ▲ Methyl groups of CNXyl ligand in **Cu-N₃** complex. ● Methyl groups in the formed Cu(I) triazole complex.

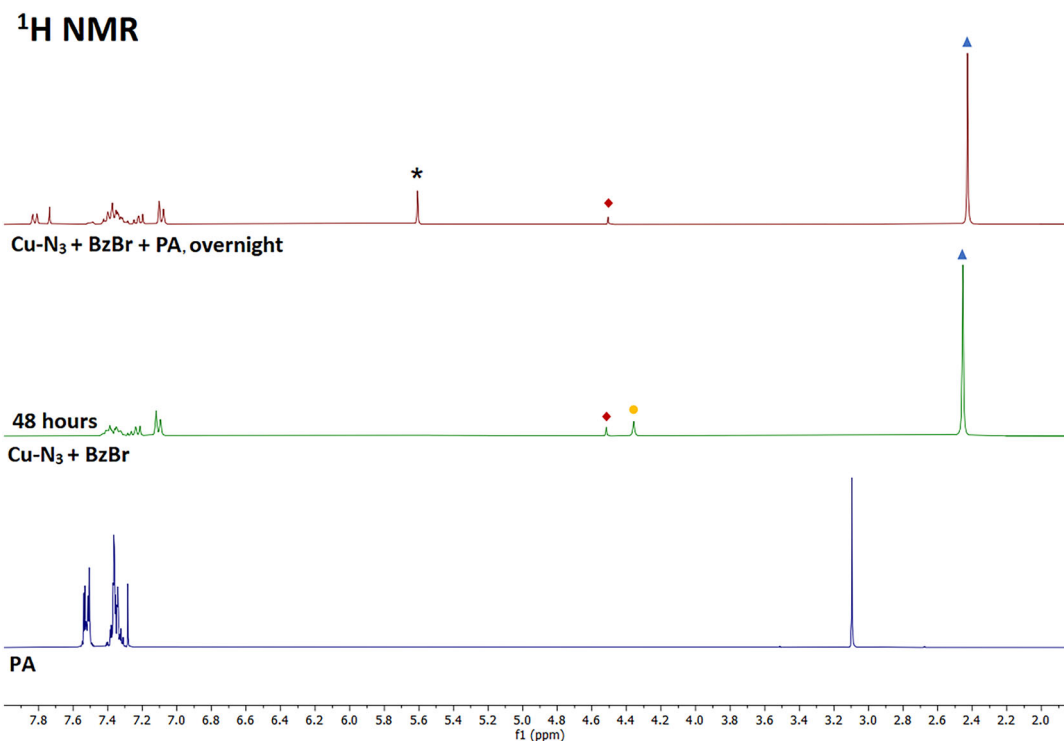


FIGURE 5 ^1H NMR spectra of phenylacetylene (PA), Cu-N_3 + benzyl bromide (BzBr) after 48 h and Cu-N_3 + BzBr + PA overnight (300 MHz, CDCl_3 , 298 K). \blacktriangle Methyl groups of CNXyl ligand in Cu-N_3 complex. \bullet Methylene group in BzBz. \blacklozenge Methylene group in BzN₃. *Methylene group in the formed triazole.

the N_3^- pseudohalide can show unusual activity. The stability of the Cu-N_3 complex towards the azide substrates was investigated by performing an intramolecular CuAAC by adding a stoichiometric amount of PA (see Scheme 4). Similarly to what was observed for $[\text{CuN}_3(\text{IPr})]$,³³ no reaction occurred even after days at moderate temperatures. Instead, using a highly activated internal alkyne such as DMAD, the corresponding triazole was formed at room temperature, as observed in the ^1H NMR monitoring shown in Figure 4. After the addition, the singlet of the CH_3 groups in DMAD is shifted to 3.88 ppm (see the NMR characterization in Figures S47–S48). The displacement of the isocyanide ligand protons also indicates the conversion of the metal complex into a compound with the triazole incorporated in the final structure and not just the free ligand. Attempts to crystallise the final product were not successful. This experiment confirmed the stability of the complex on substrates with terminal alkyne groups but not on those bearing strong electron-withdrawing groups.

A second reactivity test was carried out in a two-step reaction. In an NMR tube, a stoichiometric amount of BzBr was added to a Cu-N_3 solution in CDCl_3 . The solution was allowed to react for 2 days at room temperature to afford the corresponding benzyl azide (see NMR monitoring and characterization in Figures S49–S51).

Afterwards, PA was added in a ratio of 1:1 with respect to the Cu(I) centre. As observable in Figure 5, after one night, the singlets detectable at 5.61 and 7.74 ppm are diagnostic for the formation of the triazole. The former integrates two protons and is related to the $-\text{CH}_2$ of the benzyl moiety, while the latter is associated with the $-\text{CH}$ proton of the five-membered triazole ring. Free 1-benzyl-4-phenyl-1H-1,2,3-triazole was recovered as crystals from the NMR tube after the evaporation of the solvent. Hence, Cu-N_3 is sensitive to bromide substrates and can promote the stoichiometric alkyne cycloaddition via nucleophilic substitution.

4 | CONCLUSION

In summary, we have prepared three isocyanide Cu(I) complexes bearing pseudohalides within the coordination sphere. OCN^- and N_3^- displayed EO coordination modes, which resulted in unexpected dimeric and tetrameric geometries, confirmed by XRD. Both complexes were active towards the CuAAC. Specifically, Cu-N_3 allowed the preparation of a wide substrate scope with excellent yields using a low catalyst loading (0.5 mol%) and in mild reaction conditions, including challenging and less accessible alkynes with

terminal alcohols, where instead the previously reported [Cu(CNXyl)₃]BF₄ failed. The substrate scope reported in this study is broader than any other example reported for Cu(I) isocyanide complexes, giving important indications on the role of multinuclear species. Reactivity studies showed the robustness of **Cu-N₃** towards the stoichiometric addition of terminal alkynes to promote intramolecular CuAAC. In contrast, the reaction with activated DMAD showed complete conversion into the corresponding triazole complex. The *one-pot* synthesis of similar derivatives by intermolecular CuAAC with other internal alkynes is currently under investigation and will be submitted for publication in the near future. Additionally, intramolecular CuAAC was achieved when the coordinated EO azido ligands were first converted into the corresponding organic azide by nucleophilic attack on bromide substrates. The azide intermediate formed in situ allowed the formation of the final *click*-reaction product. Further mechanistic studies regarding the CuAAC mechanism are currently under investigation in our research group. We anticipate that the promising results obtained with **Cu-N₃** represent the starting point of a brighter future for μ_2 -bridging pseudohalide Cu(I) isocyanide complexes.

AUTHOR CONTRIBUTIONS

All the authors contributed equally to this work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.


DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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