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ARTICLE

Copper complexes bearing NHC-calixarene unit: synthesis and application in click chemistry.

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The synthesis of N-heterocyclic carbene (NHC) copper complexes supported by calix[4]arene was reported. A mono-substituted calix[4]arene was prepared through conventional procedures, followed by the attachment of imidazolyl group to compose the precursor of NHC ligands. Alkylation with two alkyl bromides followed by metalation gave fully characterized original complexes. The X-ray structure showed an « out » conformation for the copper. Catalytic activity was studied in click chemistry, which revealed good performance. In particular, three new triazoles were synthesized in high yields, solvent-free conditions and fast reaction time. The new synthesized chiral complex was tested in kinetic resolution of racemic azide.

Introduction

Organometallic chemistry is one of the most promising field for the increase of clean and sustainable catalytic processes. The development of a catalytic system greatly depends on ligands, which protect the metal centre and change its electronic, steric hindrance and solubility properties. Phosphines were popular ligands, but since the early 2000s, the N-heterocyclic carbene (NHC) family has attracted increasing attention. NHC have become significantly interesting because of their steric and electronic properties, which outperform oxidative addition and reductive elimination, minimizing ligand dissociation steps. Bulkiness, strong σ-donor and ambivalent π-bonding characters make the specific nature of the metal-carbene bond[1-6]. NHC are able to facilitate an incredible range of chemical reactions. For example, these air stable species are known to catalyse alkenes and alkynes functionalization, C-heteroatom bond formation, C-H activation as well as cycloaddition[7-14]. Furthermore, water-soluble NHC complexes can perform a wide range of reactions[15-18]. NHC ligands are also used as promising components for medicinal and material applications[19]. Numerous routes to NHC precursors offer easy design of unsymmetrical NHC, and much effort is dedicated to introduce chirality in order to develop asymmetric reactions[20-23]. Among them, the synthesis of imidazolylidene and imidazolydene has focused attention on various groups. In 2010, Cu_2O was proposed as the copper source in mild conditions[24]. Then, in 2013, copper(I) oxide is replaced by copper(I) halide to generate [(NHC)CuX] complexes[25], while Cisnetti *et al*. used ammoniac as solvent[26,27]. Later, copper powder was used directly as the copper source in 2015[28]. At the same time, easy access to homoleptic and heteroleptic NHC complexes was developed[29,30]. Using another route to unsymmetrical imidazoliums salts, Mauduit *et al*. added chiral arm on an NHC moiety thanks to amino acid and alcohols, which binded to the copper[31]. Supramolecular platform offers easy access to evolved and multi-function ligands. Among them, calix[4]arenes are attractive candidates for the design of sophisticated ligands[32-36]. Upper and narrow rim functionalization allows complex skeleton to be built, displaying advantages such as bulkiness, chimioselectivity, as well as wide complexation. The cavity can interact with a metallic centre, inducing a supramolecular effect. To combine the strengths of an NHC ligand and the calix[4]arene could lead to selective and efficient catalysts[37,38], for which a chiral feature can cooperate with the supramolecular impact of the cavity. In fact, complexation of organic guest such as alkyne by the cavity could be of particular importance to develop efficient catalysis, so calix[4]arene are potential applicants to catalyse reaction involving alkyne, for example [3+2] cycloaddition. This famous "click" reaction of azide with alkyne is a convenient route to triazole. Pharmaceutical and biological industries are interested in this family of heterocycle, because of many potential applications[39-42]. Copper NHC has recently showed a good performance as the catalyst for [3+2] cycloadditions[43-46]. As calix[4]arene-NHC palladium complexes recently showed high catalytic activity and impressive TON in Suzuki coupling[38], calix[4]arene-NHC copper complexes with similar structure could be good catalysts for [3+2] cycloaddition.

Herein, the preparation of two NHC copper complexes bearing calix[4]arene moiety is reported. The catalytic activity was evaluated in click chemistry. New triazoles were synthesized

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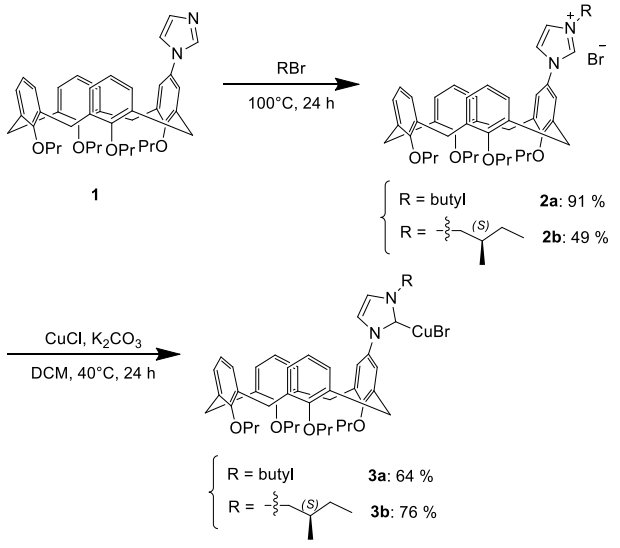
and chiral complex was tested in kinetic resolution of racemic azide.

Results and discussion

Complexes synthesis

As illustrated in scheme 1, two calix[4]arene-NHC copper complexes were synthesized in two steps from the corresponding calix[4]arene derivative **1**. This intermediate was prepared according to the literature procedure[38], in a 47% overall yield in 6 steps. Then, the imidazolyl group was alkylated with two alkyl bromides. (S)-1-bromo-2-methylbutane was chosen as the chiral source and bromobutane as the non-chiral analogue. As a result, the salt **2a** was synthesized in 91% yield, and the new salt **2b** was synthesized in 49% yield. The NMR analysis showed characteristic acidic protons of imidazolium salts, respectively at δ = 10.45 and 10.47 ppm, precursors of NHC ligands, as described in literature for the same class of compounds[38,47,48]. These protons are sufficiently acid to generate *in situ* the corresponding carbenes. Copper complexes were obtained through weak base deprotonation and direct coordination to copper source. Various conditions were tested, but only the method described by Matt *et al*[49] with K_2CO_3 in dichloromethane avoided the formation of a mixture, with no possible purification, as seen in table 1. A mixture of [(NHC)CuX] and undesired dimerised $[(NHC)_2Cu]^+$ species was a frequent reported issue for copper NHC synthesis, usually dimerised product are obtained in high temperature and long-time reaction as thermodynamic product[27,28]. The balance between the two forms can be rationalized by the bulkiness of the NHC and the difference of energy between singlet and triplet state[50]. In the first attempts, as can be seen in entry 1, 2 and 3, copper powder and copper(I) oxide were used as the copper source. Unfortunately, conversion of starting material was uncompleted, and gave several products. We supposed that the products were mono and bis NHC complexes, and probably a structure bearing an hydroxo moiety, as attested by a singlet proton around δ = 9 ppm in NMR, which was different from the acidic imidazolium proton at δ = 10.4 ppm. Formation of hydroxo complex with NHC was reported in literature[26].



Scheme 1. Synthesis of copper complexes **3a** and **3b.**

Table 1. Metalation of **2a** (reaction time = 24 h)

Entry	Conditions	Solvent	Temperature (°C)	Observations
1	$Cu_{(s)}$	MeCN	55	mixture
2	Cu_2O	DCM	40	mixture
3	Cu_2O	Toluene	110	mixture
4	CuBr, K_2CO_3	DCM	40	no reaction
5	CuCl, K_2CO_3	DCM	40	[(NHC)CuBr] 100% conversion

Then we turned our attention to another way. CuBr was used to access the bromide copper complex. But as CuBr was not soluble enough in dichloromethane, no conversion was observed so CuCl was used. In the condition of entry 5, complexes **3a** and **3b** were obtained in 64% and 76% yield respectively. This mild-condition avoided the use of a strong base as well as the use of inert atmosphere, which made the complex easier to create[51,52]. An anion metathesis occurred to exchange the chloride atom by the bromide atom, although chloride complexes are more stable than bromide complexes, because KCl salt was less soluble than KBr salt in dichloromethane that is why the equilibrium is displaced in favour of our bromide complexes. In addition, complexes were obtained by easy precipitation in pentane, as calix[4]arene moiety brought a low solubility in the pentane, and no additional recrystallization was required. Furthermore, imidazolium salts could be recycled and reengaged in the reaction, as the reaction proceed cleanly and gave no side products. In fact, calix[4]arene derivatives are particularly stable. Elemental analysis and X-ray structures confirmed that bromide is linked to the copper for **3a**. All those new structures were characterized through NMR spectroscopy. $ArCH_2Ar$ signals of compounds 2-3 appeared between 33-30 ppm in the ^{13}C NMR, and ^1H NMR revealed AB patterns for the corresponding diastereotopic protons. Both observations demonstrated that the skeleton of these calix[4]arenes are in cone conformation. **2b** and **3b** showed two characteristic sets of diastereotopics CH_2 protons around 4.00 and 1.25 ppm corresponding to the chiral side arm. No chirality transfer could be observed in NMR from the chiral side arm to neither imidazolyl protons nor calix[4]arene aromatic protons. Both complexes showed excellent stability in the air and in solution. The calix[4]arene unit protected the metallic centre from any oxidation and modification, which complemented the strong metal-NHC bond. Indeed the NHC bond occupies one binding site of the copper, and the macrocyclic cavity sterically protects the copper atom. Indeed its binding sites are more interested in host binding interaction than coordination and reaction with water or air.

X-ray analysis

A single crystal from **3a** was obtained. The X-ray analysis revealed the structure of a monomeric specie, in cone conformation for the backbone and in an out conformation for the metal centre, as can be seen in figure 1. No interactions between copper centres were observed in the packing. The Cu-C and Cu-Br bond lengths are 1.87(7) Å and 2.19(1) Å respectively.

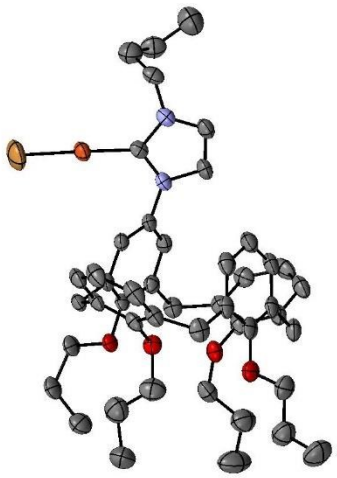


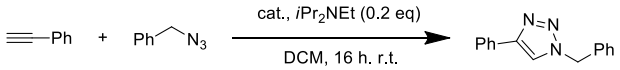
Figure 1. X-ray structure of **3a.**

The metal-C bond is slightly closer than for the palladium (1.95 Å), for the same structure[38]. Cu-C bond is included on the range of classical NHC-copper length (1.87-1.96 Å) as well as the Cu-Br bond[52]. The dihedral angle $C_{ArCalix}C_{ArCalix}N_{NHC}C_{NHC}$ is 42.8(2)°. This unusual value could be rationalized with the establishment of a weak C-H/π interaction of 4.12(1) Å between the H-imidazole and the proximal aromatic ring of the calix[4]arene centroid (see figure 38 in the supporting information). This interaction prevented the metallic centre from being as far as possible from the calix[4]arene, which could be particularly interesting for catalysis. Moreover, the complex adopts a slightly distorted linear geometry with C-Cu-Br angle at 177.5(2°). The parameter of steric hindrance $\%V_{bur}$ of the NHC ligand was calculated thanks to the SambVca web application[53]. The **3a** ligand was found to be less bulky than classical NHC, with a $\%V_{bur}$ of 23.8%. These slightly distorted geometry and parameter could be explained by the dissymmetric environment around the carbene. In fact, the butyl arm offsets the sterically demanding calix[4]arene moiety. In fact, (IPr) NHC had a calculated $\%V_{bur}$ of 31.6%, with an aromatic symmetrical substitution on the NHC. Only unsaturated NHC with hydrogen substitution showed a lower value of 18.8%, while methyl substitution presents a similar value of 24.9%[53]. This accessible metal centre could induce particularly interesting properties in catalysis. This structure is the first example of monomeric crystallized calix[4]-NHC-copper complex. Many attempts to obtain an X-structure from **3b** were unsuccessful. In fact, a lot of crystals were grown from several systems of solvents, but none were suitable for X-ray analysis, as they were highly disorganised. Based on the close precedent result, elemental analysis and NMR, a monomeric structure with a bromide was assumed by analogy to **3b**. We guessed that the difficulty to obtain good quality crystals for X-ray diffraction was due to the chiral environment of the molecule, preventing a long range organization between crystalline cells.

Catalysis of copper catalysed [3+2] cycloaddition between an alkyne and an azide CuAAC

The catalytic activity of **3a** and **3b** was evaluated in the preparation of [1,2,3]-triazoles by click chemistry.

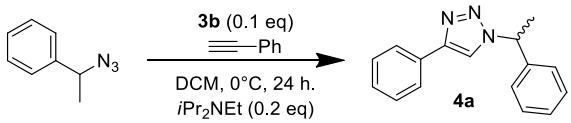
Table 2. 3a and **3b** catalysed synthesis of triazole between phenylacetylene and benzylazide



Entry	Catalyst	mol%	Conversion[a]	Yield[a]
1	**3a**	1	52%	26%
2	**3b**	1	52%	30%
3	**3a**	10	> 99%	83%
4	**3b**	10	> 99%	88%

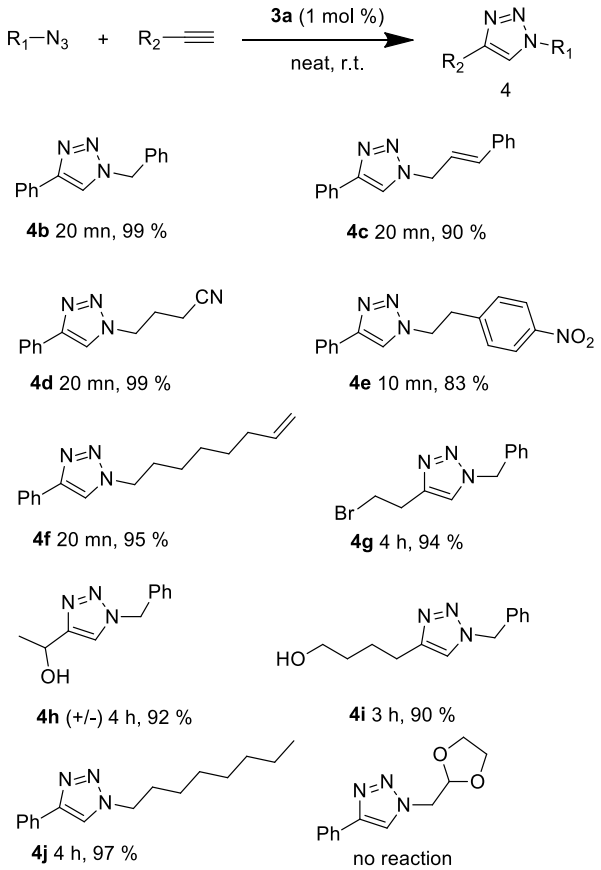
[a] determined by ^{1}H NMR with 2-methylfuran as internal standard

The results obtained for the cycloaddition between phenylacetylene and benzyl azide, two bulky substrates, are shown in table 2. The system required the use of an amine to promote the reaction, as none of the tests without base showed conversion, which is common in a non-aqueous solvent[54]. Regioselectivity is in total favour of 1,4 regioisomer, as expected. Complexes presented an appreciable catalytic activity in dichloromethane, up to 90% yield at 10 mol%, which is comparable to other catalysts in the same solvent[55,56]. Bromide derivatives are known to be particularly efficient in the CuAAC catalysis[57]. The formation of by-products such as bis-triazoles or alkynyl triazoles[58] was limited compared to direct catalysis by CuX complexes, with X=Cl, Br, I. The reactions proceeded without precaution, without inert atmosphere and distilled dichloromethane. Inspired by the work of Finn *et al*.[58], a kinetic resolution of racemic azide was therefore investigated to demonstrate the potential asymmetric catalytic activity of **3b**. The resolution was conducted between (1-azidoethyl)benzene and phenylacetylene, as shown in scheme 2. Unfortunately, no preferences between the two enantiomers of the azide were observed. Chiral HPLC clearly showed the formation of the racemic corresponding triazole. This result could be rationalized by a long distance between the chiral centre and the metal, and also by the lack of rigidity of the system, which prevented any chiral induction on the catalytic cycle. Similar strategy was ineffective in 1996[60]. The design of chiral NHC with efficient chiral induction is a challenge, as many strategies and attempts are unsuccessful[61]. **3a** was then chosen to study the scope of the reaction, because it was less expensive to synthesize and showed a similar activity to **3b**. 10 azides were prepared for this scope, among them a new azide corresponding to triazole **4f** was synthesized and fully characterized. As shown in scheme 3, a number of triazoles could be prepared in particularly high yields and short reaction times, in neat conditions and at 1 mol% of catalyst **3a**. The low-melting point triazoles required longer times than the sterically hindered others. The reaction proceeded cleanly, without side products and was easy to monitored, as the triazoles precipitated. Among them, 3 new triazoles **4d-f** were synthesized and fully characterized. No correlation between the electronic properties and the results could be established. These results are similar with the one previously obtained by Nolan *et al.*[57] with (SIMes)CuBr at 0.8 mol% (98% of yield in 20 mn for the reaction between phenylacetylene and benzyl azide, compared to 99%, scheme 3, **4b**), which highlights the performance of the NHC ligand.



Scheme 2. Kinetic resolution trial on (1-azidoethyl)benzene

The formation of triazoles in neat conditions are faster with **3a** than in solution. The reaction of phenylacetylene and benzylazide (Table 2, entry 3) gave 83% of yield compared to the 99% of yield in neat condition (scheme 3, **4b**). There are no by-products in the solvent-free catalysis, as the catalytic steps proceed faster and because the solubility of water and air in is limited. Combined with the protection of the macrocyclic cavity, it prevents any formation of by-products. Moreover, an elution on a short pad of silica transformed the complexes into their imidazolium salt. The corresponding imidazolium salts **2a** could be easily recovered by this filtration and recycled. Elution of the salt was fast thanks to the hydrophobic calix[4]arene. **2a** could then be reengaged in the metalation step to be reused. **3a** obtained by this recycling process is rigorously identical and presents the same catalytic properties as the **3a** synthetized. **2a** recovered from a silica pad is also rigorously identical as the **2a** synthesized. By this solvent-free catalysis, triazoles including functions such as bromide, cyano, linear alkane, aromatics, alkene and alcohols were prepared. This scope demonstrated the high functionality tolerance of **3a**, as only the dioxane function was not tolerated in the reaction.



Scheme 3. 3a catalysed synthesis of triazoles. Yield determined by ^{1}H NMR with 2-methylfuran as internal standard

This function could be strongly attached with the calix[4]arene cavity, avoiding catalysis. This phenomena proved the potential power of the calix[4]arene as pre-complexation unit for catalysis.

Conclusion

We have prepared and characterized the first examples of a new family of [(NHC)CuX] bearing a calix[4]arene. The two complexes were notably air stable, making them good candidates for copper catalysis. X-ray analysis showed an interesting structure for **3a**, with an unusual "out" conformation for the metal thanks to a weak C-H/π. Herein, the complexes have proved good catalytic activity in copper-catalyzed [3+2] cycloaddition, at low concentration, room temperature and in solvent-free conditions. 10 triazoles were synthesized in high yield and in short time reaction. Among them, 3 new triazoles were prepared. The potential of the catalyst was attested by the range of tolerated function of both alkyne and azide. Moreover, thanks to the stability and the properties of solubility of the calix[4]arene, the catalysts could be recycled as well as the corresponding imidazolium salts in the metalation step. Unfortunately, our first example of chiral complex was unable to separate racemic azide by kinetic resolution. This result can be rationalized through the significant distance between the chiral centre and the copper as well as the free rotation of the C-N bond for the chiral side arm. New chiral compounds from this family are currently under preparation, using the introduction of alkyl group through alkylation of imidazole derivative. We are also investigating the use of calix[6/8]arene, in order to create a supramolecular nanoreactor for click chemistry.

Experimental

Materials and methods

All commercial reagents were used as received. Solvents were dried by conventional methods. All reactions were carried out under nitrogen. Column chromatography was performed using silica gel (0.040-0.063 nm). Reactions were monitored by TLC on silica gel plate and visualized by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX at 400 or 300 MHz. *J* value are given in Hz. Mass spectra were acquired on an LCQ Advantage ion trap instrument, detecting positive ions in the ESI mode. Optical rotations were measured at 20°C by a Perkin Elmer polarimeter 343. $[\alpha]_D$ values are given in $g^{-1}.mL.dm^{-1}$. Melting points were determined by a Buchï Melting point B-540. IR spectra were recorded on a Shimadzu IRaffinity-1S spectrometer. HPLC analysis was performed on a UFLC XR- Shimadzu equipped with the Chiralcel column OD-1 (elution n-hexane / iPrOH, $V_{injection}$ = 1 µL, flow = 1 mL/mn).

Crystallography

A Suitable crystals from **3a** (N° CCDC 1476585) were selected and mounted on a Gemini kappa-geometry diffractometer (Agilent Technologies UK Ltd) equipped with an Atlas CCD detector using Mo radiation (λ = 0.71073 Å). Intensities were collected at 150 K by means of the CrysalisPro software[62]. Reflection indexing, unit-cell

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parameters refinement, Lorentz-polarization correction, peak integration and background determination were carried out with the CrysalisPro software. An analytical absorption correction was applied using the modeled faces of the crystal[63]. The resulting sets of hkl was used for structure solution and refinement. The structures were solved by direct methods with SIR97[64] and the least-square refinement on F2 was achieved with the CRYSTALS software[65]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were initially positioned geometrically and initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C---H in the range 0.93-0.98 Å) and U_{iso}(H) (in the range 1.2-1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

Synthesis of complexes 3a-b.

5-(3-butyl)-1-imidazolylium)-25,26,27,28-tetrapropyloxycalix[4]arene bromide 2a (*cone*)

The stirred mixture of **1** (0.593 g, 0.90 mmol,1.0 eq) and bromobutane (2 mL) was heated at reflux for 24 h. After cooling down to room temperature, the mixture was evaporated to dryness. The product was isolated by flash chromatography on silica gel (DCM/MeOH 100/1 to 10/1). The product was dried under vacuum to afford brown solid (651 mg, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 – 1.00 (m, 9 H, N-C-C-C-CH_3), 1.09 (q, J = 7.5 Hz, 6 H, O-C-C-CH_3), 1.36 - 1.48 (m, 2 H, N-C-C-CH_2), 1.85 – 2.01 (m, 10 H, O-C-CH_2, N-C-CH_2), 3.21 and 4.47 (AB spin systems, $^2J_{AB}$ = 13.3 Hz, 2*4 H, ArCH_2Ar), 3.68 - 3.82 (m, 4 H, O-CH_2), 3.91 – 4.08 (m, 4 H, O-CH_2), 4.53 - 4.61 (m, 2 H, N-CH_2), 6.06 (t, J = 7.5 Hz, 1 H, Ar), 6.22 - 6.28 (m, 2 H, Ar), 6.42 (m, 2 H, Ar), 6.74 (s, 1 H, N-CH), 6.87 (t, J = 7.5 Hz, 2 H, Ar), 6.98 – 7.04 (m, 2 H, Ar), 7.04 - 7.10 (m, 2 H, Ar), 7.31 (s, 1 H, N-CH), 10.45 (s, 1 H, N-CH-N) ppm, data matched with literature reference[38].

5-(3-(2(S)-methyl-butyl)-1-imidazolylium)-25,26,27,28-tetrapropylo-xycalix[4]arene bromide 2b (*cone*)

The stirred mixture of **1** (0.316 g, 0.48 mmol, 1.0 equiv) and (S)-(+)-1-Bromo-2-methylbutane (1 mL) was heated at 80°C for 48 h. The mixture was cooled down to room temperature and then evaporated. The product was isolated by flash chromatography on silica gel (DCM/MeOH 100/1 to 10/1). The product was dried under vacuum to afford pink solid (0.517 g, 49%). Mp. 153.6-156.8 °C. $[\alpha_D]^{20}$ = 0.78 g^{-1}.mL.dm^{-1} ($CHCl_3$, C = 0.51 g/mL). HRMS (ESI) $[M\text{-}Br]^+$ found 729,4601, calculated 729.4626 for $[C_{48}H_{61}N_2O_4]^+$; ^{1}H NMR (400 MHz ,$CDCl_3$) δ 0.88 - 0.96 (m, 12 H, OCCCH_3, NCC(C)CCH_3, NCC(CH_3)C), 1.03 - 1.11 (m, 6 H), 1.26 (m, 1 H, NCC(C)CH_2C), 1.45 (m, 1H, NCC(C)CH_2C), 1.85 – 2.04 (m, 9 H, OCCH_2C, NCCH(C)(C)), 3.21 and 4.47 (AB spin systems, $^2J_{AB}$ = 13.4 Hz, 2*4 H, ArCH_2Ar), 3.69 - 3.80 (m, 4 H, OCH_2C), 3.90 – 4.02 (m, 4 H, OCH_2C), 4.41 (m, 2 H, NCH_2C), 6.07 (t, J = 7.8 Hz, 1 H, Ar), 6.26 (d, J = 7.6 Hz, 2 H, Ar), 6.44 - 6.49 (m, 2 H, Ar), 6.79 (t, J = 1.8 Hz, 1 H, NCHC), 6.85 (t, J = 7.1 Hz, 2 H, Ar), 6.97 (d, J = 7.5 Hz, 2 H, Ar), 7.05 (d, J = 7.4 Hz 2 H, Ar), 7.37 (t, J = 1.7 Hz, 1 H, NCHC), 10.47 (s, 1 H, NCHN) ppm; ^{13}C NMR (400 MHz ,$CDCl_3$) δ 9.9, 10.5, 10.6, 11.1, 16.3, 22.3, 23.0, 23.3, 23.4, 26.3, 30.9, 30.9, 35.7, 55.6, 76.6, 77.2, 120.3, 121.1, 121.1, 121.2, 122.2, 122.4, 127.2, 127.3, 128.3, 128.9, 128.9, 129.1, 134.2, 134.2, 135.3, 136.0, 136.3, 136.3, 137.0, 137.1, 156.0, 157.2, 157.3 ppm; IR ν_{max}/cm^{-1} 624.9, 729.1, 758.0, 800.5, 833.2, 875.7, 889.2, 964.4, 1003.0, 1035.8, 1066.6, 1087.8, 1161.1, 1195.9, 1244.1, 1292.3, 1383.0, 1452.4, 1548.5, 2873.9, 2933.7, 2960.7

[5-(3-Butylimidazol-2-yliden-1-yl)-25,26,27,28-tetrapropyloxy-calix[4]arene] copper bromide 3a (*cone*)

A suspension of the corresponding imidazolium bromide salt **2a** (0.530 g, 0.67 mmol), finely crushed K_2CO_3 (1.256 g, 9.55 mmol) and CuCl (0.098 g, 0.98 mmol) in CH_2Cl_2 (26 mL) was stirred at 40°C under nitrogen atmosphere overnight. The completion is monitored by NMR. The mixture was filtered through a filter paper and the filter was washed with CH_2Cl_2 (3 x 10 mL). The filtrate was concentrated under vacuum to a minimum. Pentane (20 mL) was added and the resulting white precipitate was decanted. After removal of the supernatant, the solid was washed with pentane (3 x 5 mL), then dried under vacuum to afford pure white solid (0.367 g, 64%); Mp. 113.4-116.5 °C; elemental analysis found: C, 63.8; H, 6.95; N, 3.25% $C_{47}H_{58}BrCuN_2O_4$ requires C, 65.76; H, 6.81; N, 3.26%. Crystals suitable for X-ray analysis were grown by slow cooling of a solution of the complex in hot acetonitrile. ^{1}H NMR (400 MHz ,$CDCl_3$) δ 0.95 (m, 9 H, OCCCH_3, NCCCCH_3), 1.04 - 1.13 (m, 6 H, OCCCH_3), 1.30 - 1.39 (m, 2 H, NCCCH_2C), 1.78 - 1.86 (m, 2 H, NCCH_2C), 1.93 (m, 8 H, OCCH_2C), 3.20 and 4.48 (AB spin systems, $^2J_{AB}$ = 13.3 Hz, 2*4 H, ArCH_2Ar), 3.70 - 3.83 (m, 4 H, OCH_2C), 3.93 – 4.03 (m, 4 H, OCH_2C), 4.12 (t, J = 7.2 Hz, 2 H, N-CH_2C), 6.13 (m, 1 H, Ar), 6.26 (d, J = 7.2 Hz, 2 H, Ar), 6.48 (m, 2 H, Ar), 6.53 (d, J = 3.8 Hz, 1H, NCHC), 6.82 (t, J = 7.3 Hz, 2 H, Ar), 6.86 (d, J = 3.9 Hz, 1H, NCHC), 6.93 – 7.07 (m, 4 H, Ar) ppm; ^{13}C NMR (400 MHz ,$CDCl_3$) δ 9.9, 10.6, 10.6, 13.6, 14.0, 19.7, 22.3, 23.0, 23.4, 23.4, 30.9, 31.0, 33.4, 34.1, 51.5, 76.6, 76.9, 77.1, 77.2, 119.9, 120.6, 121.5, 122.1, 127.3, 128.9, 133.5, 134.1, 135.7, 135.8, 136.3, 155.8, 157.4 ppm; IR ν_{max}/cm^{-1} 675.1, 748.4, 877.6, 962.5, 1004.9, 1035.8, 1062.8, 1085.9, 1099.4, 1244.1, 1292.3, 1383.0, 1433.1, 1452.4, 1477.5, 1585.5, 2873.9, 2929.9, 2958.9

[5-(3-(2(S)-methyl-butyl)imidazol-2-yliden-1-yl)-25,26,27,28-tetrapro-pyloxycalix[4]arene] 3b copper bromide (*cone*)

A suspension of the corresponding imidazolium bromide salt **2b** (0.210 g, 0.26 mmol), finely crushed K_2CO_3 (0.152 g, 3.71 mmol) and CuCl (0.037 g, 0.38 mmol) in CH_2Cl_2 (8 mL) was stirred at 40°C under nitrogen atmosphere overnight. The completion is monitored by NMR. The mixture was filtered through a filter paper and the filter was washed with CH_2Cl_2 (3 x 10 mL). The filtrate was concentrated under vacuum to a minimum. Pentane (20 mL) was added and the resulting white precipitate was decanted. After removal of the supernatant, the solid was washed with pentane (3 x 5 mL), then dried under vacuum to afford pure white solid (0.172 g, 76%); Mp. 124.8-128.1°C, $[\alpha_D]^{20}$ = 0.68 g^{-1}.mL.dm^{-1} ($CHCl_3$, C = 1.03 g/mL). elemental analysis found: 65.38; H, 7.03; N, 3.27% $C_{48}H_{60}BrCuN_2O_4$ requires C, 66.08; H, 6.93; N, 3.21%. ^{1}H NMR (400 MHz ,$CDCl_3$) δ 0.90 - 0.96 (m, 12 H, OCCCH_3, NC(CH_3)C, NC(C)CCH_3), 1.04 - 1.12 (m, 6 H, OCCCH_3), 1.16 - 1.25 (m, 1 H, NC(C)CH_2C), 1.35 - 1.44 (m, 1 H, NC(C)CH_2C), 1.88 – 2.00 (m, 9 H, OCCH_2, NCCH(C)(C)), 3.20 and 4.48 (AB spin systems, $^2J_{AB}$ = 13.3 Hz, 2*4 H, ArCH_2Ar), 3.72 - 3.82 (m, 4 H, OCH_2C), 3.88 – 4.05 (m, 6 H, OCH_2C, NCH_2C), 6.13 (t, J = 7.8 Hz, 1 H, Ar), 6.51 (m, 2 H, Ar), 6.27 (d, J = 7.6 Hz, 2 H, Ar), 6.55 (d, J = 1.7 Hz, 1 H, NCHC), 6.83 (t, J = 7.1 Hz, 2 H, Ar), 6.84 - 6.85 (m, 1 H, NCHC), 6.95 (dd, J = 1.5, 7.6 Hz, 2 H, Ar), 7.00 - 7.05 (m, 2 H, Ar) ppm; ^{13}C NMR (400 MHz ,$CDCl_3$) δ 10.0, 10.6, 10.6, 11.2, 16.9, 23.0, 23.4, 23.4,

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26.7, 30.9, 31.0, 36.6, 57.6, 76.6, 76.9, 77.1, 77.2, 120.4, 120.5, 121.5, 122.1, 122.1, 127.3, 128.9, 133.4, 134.2, 135.7, 135.7, 136.3, 155.9, 155.9, 157.3 ppm; IR ν_{max}/cm^{-1} 667.4, 702.1, 736.8, 756.1, 763.8, 871.8, 962.5, 1004.9, 1035.8, 1064.7, 1084.0, 1097.5, 1157.3, 1192.0, 1211.3, 1226.7, 1244.1, 1292.3, 1383.0, 1545.3, 1585.5, 2873.9, 2916.4, 2929.9, 2960.7

General procedure for azide synthesis

A mixture of sodium azide (0.715 g, 11 mmol, 1.1 eq) and alkyl bromide (10 mmol, 1 eq) in DMSO (22 mL) was stirred overnight. The reaction was quenched with H_2O (50 mL), and extracted with Et_2O (3 x 30 mL). The organic phase was washed with H_2O (2 x 30 mL) and brine (30 mL), and then was dried (Mg_2SO_4) and filtered. The solvent was removed by vacuum to afford pure alkyl azides[66].

Synthesis of azide

(azidomethyl)benzene

Obtained as a colorless oil (1.330 g, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (s, 2 H, CH_2), 7.28 - 7.47 (m, 5 H, Ar), ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 54.7, 128.2, 128.2, 128.8 ppm. Data matched with literature reference[66].

(1-azidoethyl)benzene

Obtained as a colorless oil (1.450 g, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, J = 6.8 Hz, 3 H, CH_3), 4.51 (q, J = 6.9 Hz, 1 H, CH), 7.14 - 7.32 (m, 5 H, Ar) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.5, 61.0, 126.3, 128.0, 128.7, 140.8 ppm. Data matched with literature reference[66].

(E)-(3-azidoprop-1-en-1-yl)benzene

Obtained as a yellow oil (1.389 g, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (d, J = 7.0 Hz, 2 H, CH_2-N_3), 6.28 (td, J = 6.6, 15.0 Hz, 1 H, CH=C-Ar), 6.70 (d, J = 15.8 Hz, 1 H, C=CH-Ar), 7.28 - 7.48 (m, 5 H, Ar) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 52.9, 122.3, 126.6, 128.6, 134.4, 135.9 ppm. Data matched with literature reference[66].

4-azidobutanenitrile

Obtained as a colorless oil (0.667 g, 61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (quin, J = 7.0 Hz, 2 H, C-CH_2-C), 2.42 (t, J = 7.5 Hz, 2 H, CH_2-N_3), 3.43 (t, J = 6.4 Hz, 2 H, CH_2-CN) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.2, 24.6, 49.3, 118.5 ppm. Data matched with literature reference[67].

1-(2-azidoethyl)-4-nitrobenzene

Obtained as a colorless oil (1.702 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (t, J = 6.9 Hz, 2 H, CH_2-Ar), 3.59 (t, J = 6.9 Hz, 2 H, CH_2-N_3), 7.40 (d, J = 9.0 Hz, 2 H, Ar), 8.17 (d, J = 8.8 Hz, 2 H, Ar) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 35.0, 51.6, 123.7, 126.7, 129.6 ppm. Data matched with literature reference[68].

8-azidooct-1-ene

Obtained as a yellow oil (1.357 g, 89%), HRMS (EI) $[M+H]^+$ found 152.1179, calculated 152.1183 for $[C_8H_{14}N_3]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 - 1.46 (m, 6 H, CH_2), 1.59 (quin, J = 7.0 Hz, 2 H, CH_2), 2.05 (q, J = 6.6 Hz, 2 H, CH_2-C=C), 3.25 (t, J = 7.0 Hz, 2 H, CH_2-N_3), 4.89 – 5.04 (m, 2 H, C=CH_2), 5.69 - 5.87 (m, 1 H, C-CH=C) ppm; ^{13}C NMR (400 MHz, CDCl3) δ 26.4, 28.5, 28.6, 28.7, 33.5, 51.3, 114.2, 138.7 ppm; IR ν_{max}/cm^{-1} 1259.5, 1280.7, 1348.2, 1442.7, 1542.4, 1639.5, 2097.5, 2856.6, 2929.9

1-azidooctane

Obtained as a colorless oil (1.441 g, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3 H, CH_3), 1.25 - 1.42 (m, 10 H, CH_2), 1.60 (quin, J = 7.3 Hz, 2 H, CH_2-C-N_3), 3.25 (t, J = 7.0 Hz, 2 H, CH_2-N_3) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.0, 22.6, 26.7, 28.8, 29.1, 31.7, 51.4 ppm. Data matched with literature reference[66].

2-(azidomethyl)-1,3-dioxolane

Obtained as an orange oil (1.077 g, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30 - 3.37 (m, 2 H, CH_2-N_3), 3.85 – 4.03 (m, 4 H, O-CH_2-CH_2-O), 5.04 - 5.11 (m, 1 H, O-CH-O) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 32.3, 65.4, 101.8 ppm. Data matched with literature reference[69].

General procedure for catalysis in dichloromethane (4a)

To a solution of alkyne (0.1 mmol, 1 eq) in dichloromethane (1.5 mL) was added **3a** (8.7 mg, 0.01 mmol, 0.1 eq) or **3b** (8.6 mg, 0.01 mmol, 0.1 eq). The mixture was stirred for 5 minutes, and azide was added. (0.1 mmol, 1 eq). *i*Pr_2NEt was then added (3.48 µL, 0.02 mmol, 0.2 eq) and the mixture was stirred at room temperature. Conversion was monitored by ^{1}H NMR.

General procedure for solvent-free catalysis (4b-j)

Alkyne (1 mmol, 1 eq) and **3a** (8.7 mg, 0.01 mmol, 0.01 eq) were charged in a vial. Azide (1 mmol, 1 eq) was added and the resulting solution was stored at room temperature. Conversion was monitored by ^{1}H NMR. The product was isolated by flash chromatography on silica gel (pentane / ethyl acetate 100/1 to 1/1).

Synthesis of triazoles 4a-j

(+/-) 4-phenyl-1-(1-phenylethyl)-1H-1,2,3-triazole 4a

White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (d, J = 7.2 Hz, 3 H, CH_3), 5.88 (q, J = 7.2 Hz, 1 H, CH), 7.28 - 7.41 (m, 8 H, Ar), 7.66 (s, 1 H, C=CH-N), 7.78 - 7.85 (m, 2 H, Ar) ppm. Retention time of both enantiomers (elution *n*-hexane / *i*PrOH 80/20) 5.27 mn and 10.28 mn. Data matched with literature reference[70].

1-benzyl-4-phenyl-1H-1,2,3-triazole 4b

White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (s, 2 H, N-CH_2-Ar), 7.31 - 7.44 (m, 8 H, Ar), 7.69 (s, 1 H, C=CH-N), 7.83 (dd, J = 1.3, 8.3 Hz, 2 H, Ar) ppm. Data matched with literature reference[71].

1-cinnamyl-4-phenyl-1H-1,2,3-triazole 4c

White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (dd, *J* = 1.3, 6.6 Hz, 2 H, CH_2-N), 6.26 - 6.31 (m, 1 H, CH=C), 6.40 (td, *J* = 6.6, 16.1 Hz, 1 H, CH=C), 7.29 - 7.46 (m, 8 H , Ar), 7.82 (s, 1 H, C=CH- N), 7.83 - 7.88 (m, 2 H) ppm. Data matched with literature reference[72].

4-(4-phenyl-1H-1,2,3-triazol-1-yl)butanenitrile 4d

White solid; HRMS (ESI) $[M+H]^+$ found 213.1127, calculated 213.1135 for $[C_{12}H_{13}N_4]^+$; Mp: 88.9-91.1°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (quin, *J* = 6.4 Hz, 2 H, C-CH_2-C), 2.43 (t, *J* = 6.4 Hz, 2 H, CH_2-CN), 4.53 (t, *J* = 6.6 Hz, 2 H, CH_2-N), 7.40 - 7.45 (m, 2 H, Ar), 7.32 - 7.37 (m, 1 H, C=CH-N), 7.78 - 7.85 (m, 3 H, Ar) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ

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14.5, 25.8, 48.2, 118.2, 120.1, 125.6, 128.3, 128.8, 130.1, 147.9 ppm, IR ν_{max}/cm^{-1} 1022.3, 1051.2, 1072.4, 1082.1, 1141.9, 1182.4, 1201.6, 1209.2, 1325.1, 1354.0, 1371.4, 1419.7, 1446.6, 1465.9, 1485.2, 2249.0,2956.9, 3099.6, 3124.7.

1-(4-nitrophenethyl)-4-phenyl-1H-1,2,3-triazole 4e

Orange white solid; HRMS (ESI) $[M+H]^+$ found 295.1188, calculated 295.1190 for $[C_{16}H_{15}N_4O_2]^+$; Mp: 177.3-179.6; ^{1}H NMR (400 MHz, DMSO) δ 3.38 (t, J = 7.3 Hz, 2 H, Ar-CH_2-C-N), 4.74 (t, J = 7.1 Hz, 2 H, CH_2-N), 7.32 (tt, J = 1.5, 7.3 Hz, 1 H, Ar), 7.48 - 7.53 (m, 2 H, Ar), 7.40 - 7.46 (m, 2 H, Ar), 7.78 - 7.82 (m, 2 H, Ar), 8.11 - 8.16 (m, 2 H, Ar), 8.55 (s, 1 H, C=CH-N) ppm; ^{13}C NMR (400 MHz, DMSO) δ 35.2, 49.9, 121.4, 123.5, 125.1, 127.8, 128.9, 130.1, 130.7, 146.0, 146.2, 146.4 ppm ; IR ν_{max}/cm^{-1} 1016.5, 1030.0, 1047.3, 1074.3, 1109.1, 1183.4, 1192.0, 1220.9, 1315.4, 1348.8, 1427.3, 1440.8, 1454.3, 1462.0, 1483.3, 1494.8, 1507.3, 1599.0

1-(oct-7-en-1-yl)-4-phenyl-1H-1,2,3-triazole 4f

White solid; Mp: 66.1-67.6°C; HRMS (ESI) $[M+H]^+$ found 256.1808, calculated 256.1808 for $[C_{16}H_{22}N_3]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 - 1.43 (m, 6 H, CH_2), 1.91 - 1.98 (m, 2 H, CH_2-C=C), 2.00 - 2.07 (m, 2 H, CH_2-C-N), 4.38 (t, J = 7.2 Hz, 2 H, CH_2-N), 4.91 – 5.03 (m, 2 H, C=CH_2), 5.73 - 5.84 (m, 1 H, C-CH=C), 7.30 - 7.36 (m, 1 H, Ar), 7.39 - 7.45 (m, 2 H, Ar), 7.75 (s, 1 H, C=CH-N), 7.82 - 7.86 (m, 2 H, Ar) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 26.3, 28.4, 28.5, 30.2, 33.5, 50.3, 114.4, 119.3, 125.6, 128.0, 128.7, 130.6, 138.6, 147.6 ppm; IR ν_{max}/cm^{-1} 1024.2, 1053.1, 1078.2, 1188.1, 1215.1, 1356.0, 1438.9, 1454.2, 1483.3, 1643.3, 2850.8, 2926.0, 3064.9, 3082.2, 3120.8

1-benzyl-4-(2-bromoethyl)-1H-1,2,3-triazole 4g

White solid; Mp: 71.9-74.3°C; HRMS (ESI) $[M+H]^+$ found 266.0283, calculated 266.0287 for $[C_{11}H_{13}BrN_3]^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 3.28 (t, J = 7.0 Hz, 2 H, CH_2-C-Br), 3.64 (t, J = 6.8 Hz, 2 H, CH_2-Br), 5.53 (s, 2 H, CH_2-N), 7.25 - 7.29 (m, 2 H, Ar), 7.34 - 7.42 (m, 4 H, Ar, C=CH-N) ppm; ^{13}C NMR (400 MHz,$CDCl_3$) δ 29.4, 31.4, 54.0, 121.6, 127.9, 128.6, 129.0, 129.4, 134.6 ppm; IR ν_{max}/cm^{-1} 1028.0, 1051.1, 1126.4, 1205.5, 1245.4, 1294.2, 1325.1, 1350.2, 1421.5, 1435.0, 1454.3, 1494.8, 1546.9, 2852.7, 2920.2, 3030.2, 3068.7, 3124.7. Data matched with literature reference[73].

(+/-) 1-(1-benzyl-1H-1,2,3-triazol-4-yl)ethanol 4h

Blue white solid ; Mp: 49.7-51.2°C; HRMS (ESI) $[M+Na]^+$ found 226.0944, calculated 226.0951 for $[C_{11}H_{13}N_3NaO]^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.51 - 1.62 (m, 3 H, CH_3), 3.29 (br. s., 1 H, OH), 5.06 (br. s., 1 H, CH), 5.49 (s, 2 H, CH_2), 7.25 - 7.29 (m, 2 H, Ar), 7.35 - 7.39 (m, 3 H, Ar), 7.42 (br. s, 1 H, C=CH-N) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) □ = 23.0, 54.1, 77.2, 120.1, 127.4, 128.0, 128.7, 129.0, 134.4, 129.0, 128.7, 128.0 ppm; IR ν_{max}/cm^{-1} 1041.6, 1055.1, 1082.1, 1132.2, 1141.9, 1182.4, 1215.1, 1253.7, 1303.9, 1334.7, 1367.5, 1441.9, 1446.6, 1465.9, 1496.8, 2968.4, 3066.8, 3124.7, 3358.1. Data matched with literature reference[74].

4-(1-benzyl-1H-1,2,3-triazol-4-yl)butan-1-ol 4i

White solid; Mp: 77.3-79.8°C; HRMS (ESI) $[M+H]^+$ found 232.1445, calculated 232.1444 for $[C_{13}H_{18}N_3O]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 - 1.67 (m, 2 H, CH_2-C-C-OH), 1.69 - 1.80 (m, 2 H, CH_2-C-OH), 2.73 (t, J = 7.5 Hz, 2 H, CH_2-C=C), 3.62 - 3.71 (m, 2 H, CH_2-OH), 5.49 (s, 2 H, CH_2-N), 7.20 - 7.29 (m, 3 H, Ar, C=CH-N), 7.33 - 7.41 (m, 3 H, Ar) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.3, 25.5, 32.1, 54.0, 62.2, 120.6, 127.9, 128.6, 129.0, 129.4, 134.8 ppm ; IR ν_{max}/cm^{-1} 1030.0, 1053.5, 1131.14, 1178.5, 1215.1, 1330.9, 1431.2, 1142.7, 1492.9, 1552.7, 1726.3, 2860.4, 2934.5, 3055.2, 3107.3, 3392.8, 3344.0. Data matched with literature reference[75].

4-hexyl-1-phenyl-1H-1,2,3-triazole 4 j

White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, J = 7.0 Hz, 3 H, CH_3) 1.15 - 1.32 (m, 10 H, CH_2), 1.86 (quin, J = 7.1 Hz, 2 H, CH_2-C-N), 4.31 (t, J = 7.2 Hz, 2 H, CH_2-N), 7.23 - 7.38 (m, 3 H, Ar), 7.66 (s, 1 H, C=CH-N), 7.72 - 7.79 (m, 2 H, Ar), ppm. Data matched with literature reference[76].

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Novel N-heterocyclic carbene (NHC) copper complexes supported by calix[4]arene were synthesized showing good performance in catalytic activity in click chemistry.

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