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Copper(II) complexes supported by click generated mixed *NN*, *NO*, and *NS* 1,2,3-triazole based ligands and their catalytic activity in azide–alkyne cycloaddition†

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The preparation and characterization of four new copper(II) complexes supported by click generated mixed *NN*, *NO*, and *NS* 1,2,3-triazoles are reported. The four complexes display a 1 : 2 copper/ligand ratio and give monomeric units in the solid state. Crystal structures demonstrate that depending on the flexibility of the ligand *NX* (X = O, N, S) pendant arm, the coordination environment around the metal center can feature square planar or octahedral geometries. All four complexes are catalytically active at room temperature in a copper-catalyzed alkyne–azide cycloaddition (CuAAC) reaction using sodium ascorbate as a reducing agent and water–ethanol as a solvent mixture. Complex **8** supported by the *NS* ligand displayed the best catalytic performance of the series allowing for the easy and high yielding preparation of a variety of mono-, bis- and tris-1,2,3-triazoles under low catalyst loadings.

Introduction

Transition metal catalysis is a key instrument for both academia and industry as it provides an efficient and sustainable pathway to organic synthesis and the preparation of fine chemicals.[1] Because most of the transition metal catalyses are based on precious and highly expensive metal sources, an intensive quest for their replacement with cheaper and readily available metals is an important topic currently.[2] Ligand design has emerged as the most powerful tool in transition metal catalysis, as fundamental features such as activity, selectivity, and stability can be tuned taking advantage of the steric and electronic properties of the ligands that coordinate to the metal centers.[3] Consequently, a great deal of efforts has been directed to the discovery, tailoring, and development of new ligands for metal based catalysis.[4]

Functionalized 1,2,3-triazole derivatives have emerged as interesting ligands for transition metals and organometallic species due to their potential to act as N donors.[5] A wide range of mono-, bis-, tris-, and polydentate ligands containing the 1,2,3-triazole skeleton has been synthesized and studied for their coordination chemistry.[6] The preparation of this type of ligands has become more accessible due to the discovery of the 1,3-dipolar Cu(I) catalyzed alkyne–azide cycloaddition (CuAAC) reaction which yields 1,4-disubstituted 1,2,3-triazoles.[7] This multicomponent one-pot process offers great advantages such as simplicity, reliability and high atom economy. Ligands synthesized through the CuAAC reaction have found extensive use in coordination chemistry recently.[8] Their corresponding metal complexes have been studied for their electron transfer and magnetic properties,[9] and used as metallo-supramolecular assemblies[10] and as homogeneous catalysts.[11]

Development of hybrid *NX* triazole (X = N, O, S) ligands has attracted recent attention due to the enhanced coordination capability offered by the heteroatom pair of electrons which is available for donation to the metal center.[12] Due to the prospective bi- or multidentate coordination of the mixed *NX* (X = N, S) triazoles, the stability and catalytic properties of the metal derivatives are usually improved when compared to monodentate systems.[13]

As part of our interest in developing the coordination chemistry of various click-derived ligands and exploring the application of the respective metal complexes, we present

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† Electronic supplementary information (ESI) available: Sample ^{1}H and ^{13}C NMR for mono-, bis- and tris-1,2,3-triazoles prepared by the CuAAC process. CCDC 974373–974375 for complexes **5**, **6**, and **8**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4dt00323c

herein the synthesis and characterization of four new copper(II) complexes of the form $[Cu(L)_2Cl_2]$ supported by click synthesized mixed *NN*, *NO*, and *NS* 1,2,3-triazole ligands. Solid state characterizations are presented to illustrate the effect of the heteroatom of the triazole *N*-pendant arm in the coordination environment of the metal center. The four new complexes showed activity as catalysts in the CuAAC process using sodium ascorbate as a reducing agent. The complex supported by the mixed *NS* triazole displayed the best catalytic performance of the series, allowing for easy and high yielding preparation of a variety of mono-, bis- and tris-1,2,3-triazoles under low catalyst loadings.

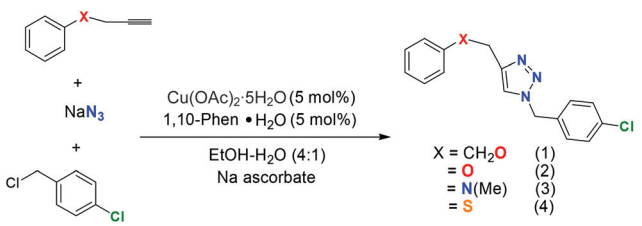
Results and discussion

Synthesis and characterization

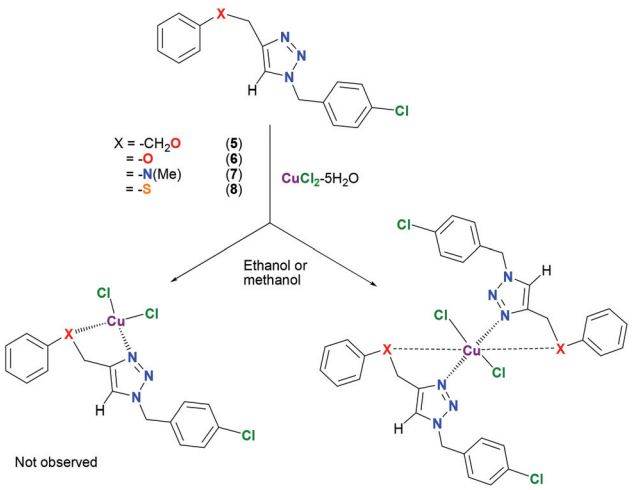
The substituted 1,2,3-triazoles used as ligands in this work were prepared through a Cu(I) catalysed process as described in the literature.[14,15] The click reaction of the appropriate alkyne and sodium azide in the presence of 4-chlorobenzyl chloride, $Cu(OAc)_2{\cdot}5H_2O$ and sodium ascorbate provided ligands **1–4** in good yields (Scheme 1).

Stirring of ligands **1–4** with equimolar amounts of $CuCl_2{\cdot}5H_2O$ in methanol or ethanol at room temperature yielded blue precipitates in the case of ligands **1** and **2** and green precipitates in the case of **3** and **4**. The copper(II) complexes were purified by filtration and washing with cold methanol. Under the above reaction conditions, we were expecting complexes with ligand/copper 1 : 1 ratios and with the $[Cu[L]Cl_2]$ formula (Scheme 2). However, the low yields (~25%) and the large amount of residual copper chloride indicated incomplete consumption of the starting materials. As no NMR data were available (paramagnetic complexes), elemental analyses were obtained, and the results unveiled a 2 : 1 ligand/metal ratio for all the complexes (Scheme 2).

Having confirmed the actual ligand/metal ratio of the synthesized complexes, we modified the reaction conditions by using two equivalents of the ligand and stirring for 12 h. The precipitates were formed, and the yields of the isolated products were increased in a range of 71 to 82%. Complexes **5–8** were characterized by melting point, FT-IR and UV-vis. The thermogravimetric (TG) curves over 25–800 °C for complexes **5–8** are given in Fig. 1. Complexes **5** and **6** are stable up to 191 and 198 °C respectively, while **7** and **8** maintain its original composition up to 251 and 215 °C. A steady decline until



Scheme 1 Synthesis of mixed ligands **1–4**.



Scheme 2 Synthesis of complexes **5–8**.

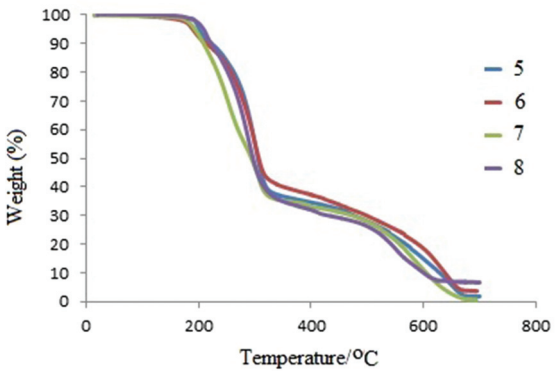


Fig. 1 TGA curves for **5–8**.

reaching a residual weight for **5–8** is observed in the range of ~600 to 650 °C. As noted in Fig. 1, all the complexes display similar thermal decomposition patterns.

In order to gain further insight into the copper(II) complex structures, we focused next on the preparation of X-ray quality single crystals. Complex **5** was crystallized by slow evaporation of a concentrated DCM solution at room temperature and the solid state structure is depicted in Fig. 2. Complex **5** crystallizes

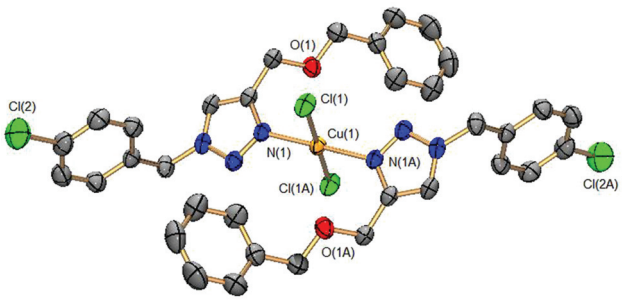


Fig. 2 ORTEP drawing of complex **5**. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.

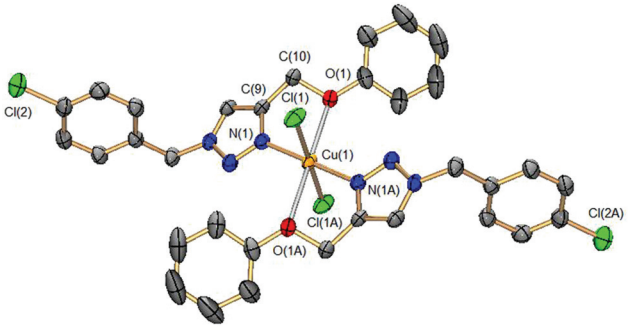


Fig. 3 ORTEP drawing of complex **6**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.

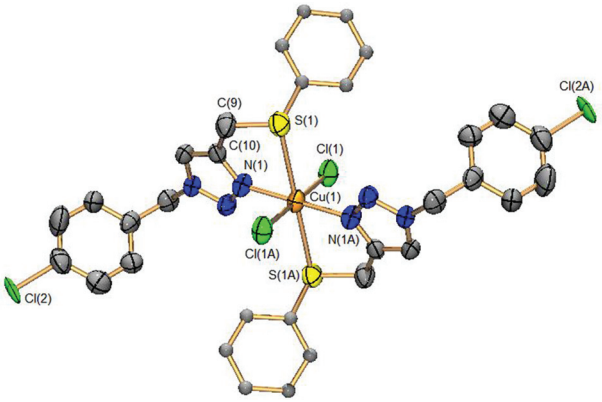


Fig. 4 Molecular structure of complex **8** shown to illustrate atom connectivity. Hydrogen atoms are omitted for clarity.

in a triclinic $P\bar{1}$ space group as a monomeric unit and confirms the 1 : 2 metal/ligand ratio previously assumed. The copper(II) center is coordinated to a single nitrogen of each of the two 1,2,3-triazole ligands with N(1)–Cu(1) and N(1A)–Cu(1) bond distances of 1.9976(16) Å and to two chlorine atoms with Cu(1)–Cl(1) and Cu(1)–Cl(1A) bond distances of 2.2504(5) Å. An overall square planar geometry around the metal center is observed. Interestingly, the O(1) and O(1A) atoms are located far away from the Cu(1) center [3.1570 Å] deterring a possible bidentated coordination of each 1,2,3-triazole ligand.

Single crystals of complex **6** were prepared by diethylether vapour diffusion into a chloroform saturated solution. Complex **6** crystallized in the triclinic $P\bar{1}$ spatial group as a monomeric unit, and the solid state structure is shown in Fig. 3. The copper center presents a coordination number of six with an octahedral geometry. Each triazole ligand coordinates the metal center in a bidentate fashion through the N(1), O(1) and N(1A)–O(1A) atoms and the two chlorine atoms complete the coordination sphere at the apical positions. The highly symmetric structure of **6** features in a *C*2 axis drawn through the two Cl(1)–Cu(1)–Cl(1A) atoms. The Cu(1)–N(1) and Cu(1)–N(1A) bond lengths are 1.9902(16) Å and the Cu(1)–O(1) and Cu(1)–O(1A) bond distances are 2.2701(6) Å, falling all in the standard distances for triazole complexes.[16] The bidentate fashion of the 1,2,3-triazole ligands in complex **6** may be related to the more rigid structure and proximity of the ArO-moiety instead of the more flexible $ArCH_2O$-moiety displayed in complex **5**. The Cu(1) center forms a five-membered ring with O(1), C(10), C(9) and N(1) with an overall conformation best described as an envelope.

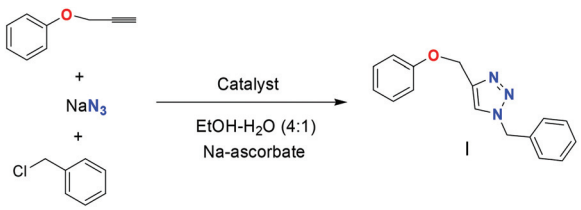
Despite the various attempts to crystallize complexes **7** and **8**, we were not able to obtain appropriate X-ray quality samples. The best set of single crystals for complex **8** was obtained by slow evaporation of a methanol solution at room temperature yielding needle shaped green samples. Although full refinement could not be obtained due to the crystal quality,[17] the molecular structure and the atom connectivity of complex **8** (Fig. 4) are unambiguous and allow its discussion and solid state comparison. Complex **8** resembles the molecular structure of **6** featuring a monomeric unit that presents a *C*2 axis drawn through the Cl(1)–Cu(1)–Cl(1A) atoms. Each triazole ligand displays a bidentate coordination through the N(1) and S(1) atoms providing a hexacoordinated copper center with an overall octahedral geometry. The five membered ring formed by the S(1), C(9), C(10), N(1) and Cu(1) atoms also resembles the envelope shape displayed in complex **6**.

The d^9 electronic configuration of the metal center does not affect the almost perfect square planar geometry in complex **5** (torsion angle of 0.03°). However, in complexes **6** and **8**, a tetragonal compression due to the Jahn–Teller effect is appreciable due to the elongation of the bonds in the *z*-axis drawn by the apical chlorine atoms (*z*-out distortion).

Although the crystal structure of complex **7** could not be achieved, its structure can be correlated to **8** based on the following arguments. The hard and soft (Lewis) acid and bases concept indicates that the Cu(II)–S and Cu(II)–N interactions are stronger than Cu(II)–O. This feature enforces the idea that complexes **7** and **8** display a bidentate coordination fashion towards the metal center. In ligands 1–4, there are distinct structural differences because of the lone pair on X to the aryl–π system interactions; this leads to the monodentate N-bonding in **5** whereas in **6–8**, the conformation about the C–X–C(aryl) has a preferred planar orientation facilitating the X–Cu(II) interaction. This effect will be even more pronounced in ligand **3** due to the role of the N-aryl lone pair in π-aryl–C(6) interaction. Additionally, the hardness of the ((aryl)C)–X (X = O, N or S) will be different from the possible CH_2–O–CH_2 to copper.

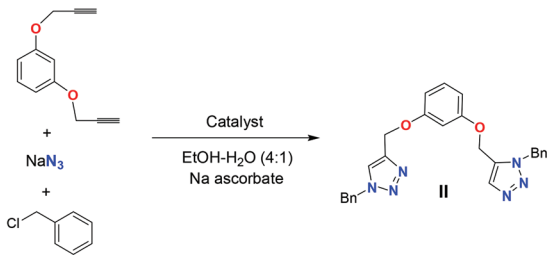
CuAAC activity of complexes 5–8

Copper(I) complexes of 1,2,3-triazoles are potential catalysts for the [2 + 3] cycloaddition reaction between azides and alkynes (CuAAC). In recent years, several hybrid *NS* ligands have been tested as catalysts for click reactions showing an improved performance compared to standard monodentate systems such as triazoles, phosphines, and imidazoles.[12,13] Knowing that our copper(II) complexes could be reduced with sodium ascorbate to render Cu(I) active species, we decided to use these *in situ* generated catalysts for the preparation of monotriazoles.



Catalyst	mol %	Na ascorbate	Time (h)	*Yield (%)
$Cu(OAc)_2{\cdot}5H_2O$	5	------	16	43
$Cu(OAc)_2{\cdot}5H_2O$	5	5 mol%	16	70
$Cu(OAc)_2{\cdot}5H_2O$	5	1.0 equiv	16	83
5	5	5 mol%	16	73
6	5	5 mol%	16	81
7	5	5 mol%	16	88
8	5	5 mol%	16	95

Scheme 3 Catalytic performance of complexes **5–8** in the synthesis of monotriazole **I**. *Isolated yield.



Catalyst	mol %	Na ascorbate	Time (h)	*Yield (%)
$Cu(OAc)_2{\cdot}5H_2O$	5	-------	16	38
$Cu(OAc)_2{\cdot}5H_2O$	5	5 mol %	16	64
$Cu(OAc)_2{\cdot}5H_2O$	5	1.0 equiv	16	71
5	5	5 mol%	16	56
6	5	5 mol%	16	67
7	5	5 mol%	16	74
8	5	5 mol%	16	83

Scheme 4 Catalytic performance of complexes 5–8 in the synthesis of bistriazole **II**. *Isolated yield.

As a first target, we tested complexes **5–8** in the three component preparation of **I** and we compared their performance with the previously reported methodology that employed $Cu(OAc)_2{\cdot}5H_2O$ as the metal source.

As depicted in Scheme 3, complexes **7** and **8** showed the best catalytic performance of the series and they even improve the reported literature procedure yield (88 and 95% yields, respectively). Complexes **5–8** displayed good solubility in water and ethanol mixture, and inert conditions were not required. The reactions proceeded smoothly at room temperature in all cases and the amount of sodium ascorbate necessary for good click reaction performance was only 5 mol%. The synthesized 1,2,3-triazole can be easily purified by a chromatographic column on silica gel using DMC and methanol (99 : 1) and the presence of the catalyst 1,2,3-triazole ligand represents no problem during purification.

Pleased by these results, we decided to challenge the capabilities of complexes **5–8** in the preparation of bis-1,2,3-triazoles of type **II**. Using similar reaction conditions to those reported for the synthesis of **II**,[15] we carried out the CuAAC reaction of 1,3-bis(prop-2-ynyloxy) benzene with sodium azide in the presence of benzyl chloride and 5 mol% of the catalyst. We observed that the performance of complexes **7** and **8** was better than those of $Cu(OAc)_2{\cdot}5H_2O$ under similar reaction conditions (Scheme 4).

The formation of bis-triazole **II** under the catalytic **5–8** is shown in Fig. 5. Conversions after four reaction hours are similar for all the catalysts. Nevertheless, as the reaction time increases, the higher efficiency of catalyst **8** is appreciable reaching conversions up to 90% in 10 h and full conversion in 12 h.

On the basis of the kinetic data and the isolated yields of **I** and **II**, the catalytic performance of the complexes reported in this paper can be ordered as **5** < **6** < **7** < **8**. To get more insights into the factors leading to catalytic performance and bearing in mind that 1,2,3-triazoles were prepared from complexes that contain the same type of ligands, the study of the catalysts' stability toward ligand/product exchange reactions was imperative.

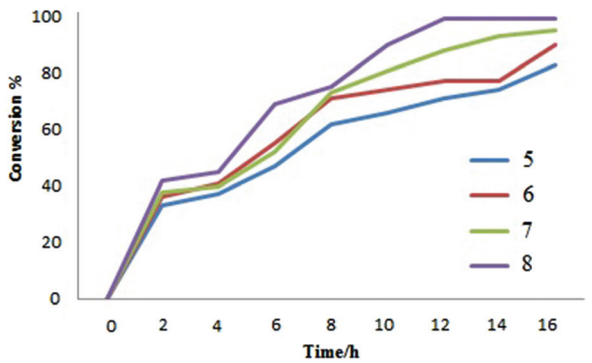


Fig. 5 Formation of **II** under the catalytic **5–8** (determined by GC-MS).

Table 1 shows the results of the reactions of **5–8** with triazoles **I** and **II** in an ethanol–water (4 : 1) solvent mixture. The reactions were performed at room temperature stirring equimolar amounts of the catalyst and the respective triazole for 16 h, and purification of products was performed by column

Table 1 Ligand exchange reactions of **5–8** with triazoles **I** and **II**

$[L_2CuCl_2] + n\text{Triazole} \longrightarrow [\text{Triazole}_n\text{-}CuCl_2] + 2L$

Catalyst	Triazole	Ligand : yield[a] (%)	Triazole	Ligand : yield[a] (%)
5	**I**	1 : 49	**II**	1 : 61
6	**I**	2 : 32	**II**	2 : 39
7	**I**	3 : 19	**II**	3 : 25
8	**I**	4 : 9	**II**	4 : 12

[a] Based on the theoretical amount of ligand contained in the original complex.

Table 2 Ligand exchange reactions of reduced **5–8** with triazoles **I** and **II**

$[L_2CuCl_2]$ + *n*Triazole —(Na ascorbate)→ $[Triazole_n$-"Cu(I)"] + 2L

Catalyst	Triazole	Ligand : yield[a] (%)	Triazole	Ligand : yield[a] (%)
5	**I**	1 : 55	**II**	1 : 66
6	**I**	2 : 41	**II**	2 : 48
7	**I**	3 : 25	**II**	3 : 31
8	**I**	4 : 13	**II**	4 : 17

[a] Based on the theoretical amount of ligand contained in the original complex.

chromatography. The results indicate the amount of released ligand that was originally contained in the copper catalyst.

Two main aspects from the data of Table 1 can be settled. First, the ligand displacement percentages of complex **5** are larger from the series reaching up to 61% with triazole **II**. Second, the exchange percentages in **5–8** are larger with **II**, likely due to a chelate effect exerted by the bis-triazole. Remarkably, the amount of released ligand **4** from complex **8** is not larger than 12% in both cases.

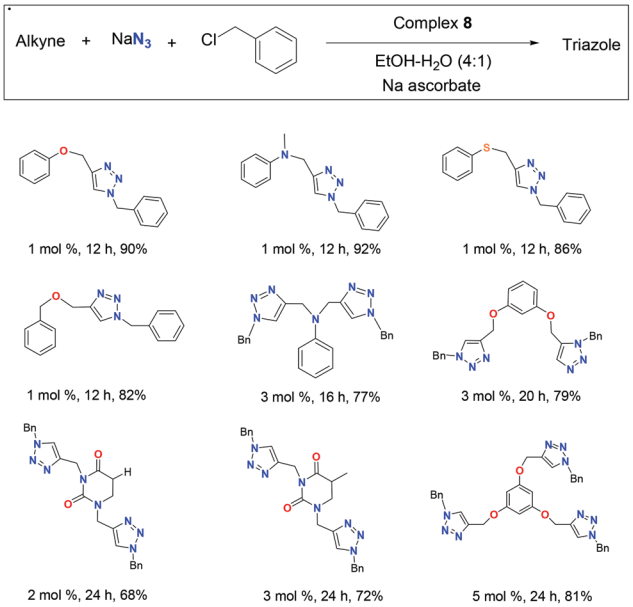
As the active catalysts for the click process are obtained after reduction with sodium ascorbate, we studied ligand exchange reactions using this *in situ* reduced "Cu(I)" species. Table 2 shows the ligand displacement percentages obtained after the reaction of the reduced **5–8** with triazoles **I** and **II**.

According to the ligand displacement percentages shown in Table 2, the reduced species are slightly more unstable in solution than the parent complexes **5–8**. Nonetheless, their overall solution behaviour is similar, displaying the reduced complex **5** as the more labile while the reduced complex **8** features the higher stability of the series (no more than 17% of ligand displacement).

With the overall results, it is arguable that the stability of the metal complex in solution is a key factor in the catalytic performance of **5–8**. For instance, complex **5** that in the solid state displayed monodentate coordination and allowed easier ligand exchange in solution results in the less effective catalyst. In contrast, the lesser ligand exchange observed in complexes **6–8** increases the conversion to products due to a more effective coordination capacity and solution stability. Particularly, the sulphur atom, being the largest and softer of the heteroatoms, results in a highly stable complex in solution which provides the best catalytic copper species of the series.

After establishing that complex **8** (*NS* mixed ligand) was the most efficient catalyst of the series, we decided to perform next a substrate screening. As observed in Scheme 5, complex **8** is capable of catalysing the formation of a series of mono-, bis- and tris-1,2,3-triazoles featuring a variety of functional groups and topologies.

The optimized synthesis of monotriazoles required only 1 mol% of the catalyst and the respective reducing agent, and no longer than 12 h was necessary to achieve good to excellent yields (82–92%). In the case of the preparation of bis-triazoles, the amount of the catalyst and the reducing agent only



Scheme 5 The range of substrates catalysed by complex **8**.

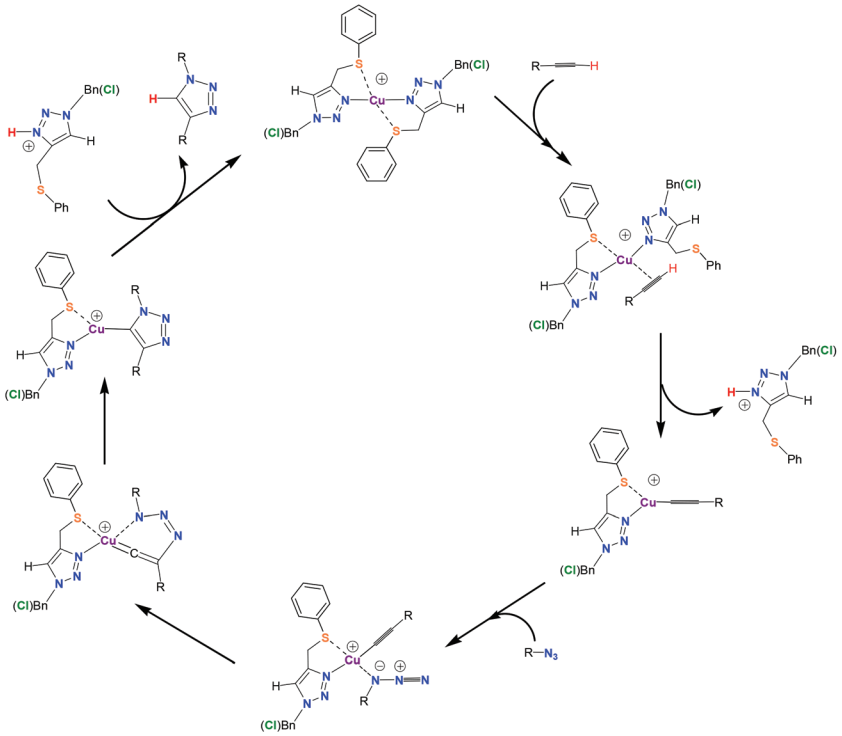
increases to 3 mol% (1.5 mol% of catalyst per triazole unit), and 18 to 24 h of stirring at room temperature is necessary to reach yields from 68 to 79%. It is important to mention that even 1,2,3-triazoles based on biologically active thymine and uracil compounds can be prepared.

The most challenging part of the substrate screening involved the preparation of a tris-1,2,3-triazole based on phloroglucinol. In this trial, 5 mol% of the catalyst and the reducing agent and 24 h of stirring at room temperature gave the highly functionalized product in 82% isolated yield.

A plausible reaction mechanism for the synthesis of 1,2,3-triazoles using complex **8** is depicted in Scheme 6. Once **8** is reduced to Cu(I) with sodium ascorbate, the mechanism is probably started by the coordination of the alkyne to the soft cationic Cu(I) center in a η^2 mode. The metal enhanced acidity of the –CH group in the alkyne moiety favours its deprotonation by one of the copper coordinated 1,2,3-triazole ligands resulting in the formation of a triazolium salt and the generation of a Cu(I)–acetylide complex. The *in situ* formed organic azide then coordinates to the highly electrophilic cationic Cu(I)–acetylide complex, and the cycloaddition takes place through the formation of a five membered ring metallo-cycle which after rearrangement yields a copper–triazolide intermediate. The subsequent protonation of the triazolide moiety by the triazolium salt releases the desired 1,2,3-triazole and regeneration of the active catalyst takes place to finish the cycle.

Conclusions

We have reported the synthesis and characterization of four new copper(II) complexes supported by click synthesized mixed *NX* (X = N,O,S) 1,2,3-triazoles. The crystal structures of



Scheme 6 Proposed reaction mechanism of complex **8** in the click process.

complexes **5**, **6**, and **8** display monomeric units and a ligand–metal ratio of 2 : 1. Complex **5** presents a square planar geometry around the metal center while complexes **6** and **8** feature octahedral coordination environments. For complexes **6** and **8** the triazole ligands coordinate the metal center in a bidentate fashion forming a five membered metallacycle with an envelope-like conformation. The four copper(II) complexes were reduced with sodium ascorbate and then tested in the CuAAC reaction.

Complexes **5**–**7** show moderate to good catalytic activity in the synthesis of mono- and bis-triazoles while complex **8** (supported by a *NS* mixed triazole) provided the best catalytic performance of the series allowing for the synthesis of a variety of mono-, bis- and tris-1,2,3-triazoles under low catalyst loadings. The present catalytic studies are appealing because the preparation of 1,2,3-triazoles could be achieved from a series of complexes that contain click produced ligands as well. The use of mixed *NX* 1,2,3-triazoles as ligands for various transition metals and their catalytic applications are under investigation in our laboratory currently.

Experimental section

General information

Commercially available reagents and solvents were used as received. Ligands **1**–**4** were synthesized as reported in the literature.[14,15] Flash column chromatography was performed on Kieselgel silica gel 60 (230–400 mesh). Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded on a Bruker Alpha FT-IR/ATR spectrometer. UV-vis analyses were obtained with an Agilent 8453 Spectrophotometer. Elemental analyses were obtained with a Thermo Finnegan CHNSO-1112 apparatus. All thermograms were performed in a SDTQ600 equipment at 20 °C min^{-1} from room temperature to 700 °C under a nitrogen flow of 5 mL min^{-1} using an alumina pan. GC-MS analyses were performed in an Agilent GC model HP 5890 coupled with a mass detector model 5973. X-Ray diffraction analyses were collected in an Agilent Gemini Diffractometer using Mo Kα radiation (l = 0.71073 Å). Data were integrated, scaled, sorted, and averaged using the CrysAlisPro software package. The structures were solved using direct methods using SHELX 97 and refined by full matrix least squares against F^2.[18] All nonhydrogen atoms were refined anisotropically. The position of the hydrogen atoms was kept fixed with common isotropic display parameters. The crystallographic data and some details of the data collection and refinement are given in Table 3. The programs ORTEP[19] and POV-Ray[20] were used to generate the X-ray structural diagrams pictured in this article.

Synthesis of complexes 5–8

Complex 5. A 3 mL methanol solution of copper chloride pentahydrate (54 mg, 0.318 mmol) was added slowly to a solution of ligand **1** (200 mg, 0.637 mmol) in 5 mL of methanol and the reaction turned blue immediately. The reaction was stirred for 12 h at room temperature and a blue precipitate appeared. The solid was collected by vacuum filtration and washed three times with 2 mL portions of cold (0 °C)

Table 3 Crystallographic data and summary of data collection and structure refinement

	5	6
Formula	$C_{34}H_{32}Cl_4CuN_6O_2$	$C_{32}H_{28}Cl_4N_6O_2$
Fw	762.00	733.94
Cryst syst	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
T (K)	293(2)	293(2)
a (Å)	7.2326(3)	7.1710(3)
b (Å)	8.3664(4)	8.3954(3)
c (Å)	15.0156(5)	14.3714(5)
α (°)	97.304(3)	75.138(3)
β (°)	102.771(3)	81.275(3)
γ (°)	98.187(3)	79.855(3)
V (Å^3)	865.186(6)	818.01(5)
Z	1	1
d_{calc}/g cm^{-3}	1.463	1.490
μ (mm^{-1})	4.063	1.034
Refl collected	19 934	24 061
T_{min}/T_{max}	0.734	0.937
N_{measd}	3441	2861
[R_{int}]	0.0414	0.0527
R [$I > 2\sigma(I)$]	0.0350	0.0335
R (all data)	0.0451	0.0394
R_w[$I > 2\sigma(I)$]	0.0899	0.1226
R_w (all data)	0.0970	0.1297
GOF	1.029	1.045

methanol. A final washing with diethyl ether and vacuum drying yielded the title product as a blue solid in 71% yield (0.226 mmol, 172 mg). Single crystals were obtained by slow evaporation of a concentrated ethanol solution. Mp = 165–167 °C. FT-IR/ATR ν_{max} cm^{-1}: 3149, 3115, 3058, 3032, 2997, 2940, 2882, 2863, 2846, 1655, 1573, 1483, 1469, 1454. UV/vis (MeOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}): 269 (6.62×10^3) 323 (1.25×10^3) 456 (2.60×10^2). Found: C, 53.42; H 4.26, N 11.07; calc. for: $C_{34}H_{32}Cl_4CuN_6O_2$ C, 53.59; H, 4.23, N 11.03.

Complex 6. A 3 mL methanol solution of copper chloride pentahydrate (57 mg, 0.333 mmol) was added slowly to a solution of ligand **2** (200 mg, 0.667 mmol) in 5 mL of methanol and the reaction turned blue immediately. The reaction was stirred for 12 h at room temperature and a blue precipitate appeared. The solid was collected by vacuum filtration and washed three times with 2 mL portions of cold (0 °C) methanol. A final washing with diethyl ether and vacuum drying yielded the title product as a blue solid in 74% yield (0.246 mmol, 181 mg). Single crystals were obtained by diethyl ether vapour diffusion into a concentrated chloroform solution of the product. Mp = 177–179 °C. FT-IR/ATR ν_{max} cm^{-1}: 3150, 3112, 3064, 1597, 1584, 1495, 1455, 1386, 1334, 1289, 1232. UV/vis (MeOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}): 250 (6.20×10^3) 328 (4.18×10^3) 453 (1.18×10^2). Found: C, 52.22; H 3.96, N 11.73. Calc. for: $C_{32}H_{28}Cl_4CuN_6O_2$ C, 52.37; H, 3.85, N 11.45.

Complex 7. A 3 mL methanol solution of copper chloride pentahydrate (55 mg, 0.319 mmol) was added slowly to a solution of ligand **2** (200 mg, 0.639 mmol) in 5 mL of methanol and the reaction turned green immediately. The reaction was stirred for 12 h at room temperature and a green precipitate appeared. The solid was collected by vacuum filtration and washed three times with 2 mL portions of cold (0 °C) methanol. A final washing with diethyl ether and vacuum drying yielded the title product as a blue solid in 77% yield (0.245 mmol, 187 mg). Mp = 156–158 °C. FT-IR/ATR ν_{max} cm^{-1}: 3161, 3215, 3168, 3042, 3000, 2974, 2788, 2633, 2122, 1675, 1612, 1584, 1488, 1457. UV/vis (MeOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}): 254 (5.63×10^3), 317 (3.14×10^3), 455 (1.34×10^2). Found: C, 53.41; H 4.17, N 14.98. Calc. for: $C_{34}H_{34}Cl_4CuN_8$ C, 53.73; H 4.51, N 14.74.

Complex 8. A 3 mL methanol solution of copper chloride pentahydrate (54 mg, 0.316 mmol) was added slowly to a solution of ligand **2** (200 mg, 0.633 mmol) in 5 mL of methanol and the reaction turned green immediately. The reaction was stirred for 12 h at room temperature and a green precipitate appeared. The solid was collected by vacuum filtration and washed three times with 2 mL portions of cold (0 °C) methanol. A final washing with diethyl ether and vacuum drying yielded the title product as a blue solid in 82% yield (0.259 mmol, 198 mg). Samples for X-ray diffraction were obtained by the slow evaporation of a concentrated methanol solution of the product. Mp = 191–193 °C. FT-IR/ATR ν_{max} cm^{-1}: 3129, 3079, 3058, 3020, 2927, 1998, 1974, 1581, 1558, 1488, 1438, 1408, 1346, 1256, 1228. UV/vis (MeOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}): 275 (5.98×10^3), 311 (3.45×10^3), 459 (1.82×10^2). Found: C, 50.30; H 3.68, N 11.00. Calc. for: $C_{32}H_{28}C_{l4}CuN_6S_2$ C, 50.17; H 3.68, N 10.97.

General procedure for the CuAAC catalysis trials

Monotriazole preparation. To a 20 mL round-bottom flask equipped with a magnetic stirrer were charged the appropriate catalyst and sodium L-ascorbate in equal mole percentages. After addition of 7 mL of a mixture of EtOH–H_2O (4 : 1 v/v), the resulting suspension was stirred for five minutes at room temperature. Subsequently, 1.14 mmol of the ligand, 1.40 mmol of sodium azide, and 1.40 mmol of benzyl chloride were added to the reaction mixture, which was stirred for 12 h at room temperature. 5 mL of H_2O was added to the reaction mixture and the precipitate was filtered off, washed thoroughly with H_2O, petroleum ether, and dried under vacuum. The crude products were purified by column chromatography, and their characterization is consistent with the literature reports.[14,15,21,22]

Bis-triazole preparation. To a 20 mL round-bottom flask equipped with a magnetic stirrer were charged the catalyst and sodium L-ascorbate in equal mole percentages (according to Scheme 4). After addition of 5 mL of a mixture of EtOH–H_2O (4 : 1 v/v), the resulting suspension was stirred for five minutes at room temperature. Subsequently, 0.70 mmol of the alkyne, 1.54 mmol of sodium azide, and 1.54 mmol of benzyl chloride were added to the reaction mixture, which was stirred at room temperature (refer to Scheme 4 for reaction times). 5 mL of H_2O was added to the reaction mixture and the precipitate was filtered off, washed thoroughly with H_2O, petroleum ether, and dried under vacuum. The crude products were purified by column chromatography and their characterization is consistent with the literature reports.[14,15,23]

Tris-triazole preparation. To a 20 mL round-bottom flask equipped with a magnetic stirrer were charged 16 mg (0.021 mmol, 5 mol%) of complex **8** and 4 mg (0.021 mmol, 5 mol%) of sodium L-ascorbate. After addition of 10 mL of a mixture of EtOH–H_2O (4 : 1 v/v), the resulting suspension was stirred for five minutes at room temperature. Subsequently, 107 mg (0.42 mmol) of 1,3,5-tris(prop-2-ynyloxy)benzene, 90 mg (1.39 mmol) of sodium azide, and 0.16 mL (1.39 mmol) of benzyl chloride were added to the reaction mixture, which was stirred for 24 h at room temperature. 10 mL of H_2O was added to the reaction mixture and the precipitate was filtered off, washed thoroughly with H_2O, petroleum ether, and dried under vacuum. The crude product was purified by column chromatography (CH_2Cl_2–MeOH 96 : 4 v/v) and its characterization is consistent with the literature.[14,24]

Ligand exchange reactions. To a 20 mL round-bottom flask equipped with a magnetic stirrer were charged 0.5 mmol of the copper complex and stoiquiometric amounts of the respective triazole **I** or **II**. After addition of 10 mL of a mixture of EtOH–H_2O (4 : 1 v/v) the resulting suspension was stirred for 16 h at room temperature. The resulting mixture was extracted with DCM, dried over $MgSO_4$ and dried under vacuum. The residue was purified by column chromatography starting with 100% CH_2Cl_2 and gradually increasing the polarity of the eluent by adding MeOH. The purified triazoles were characterized by ^{1}H and compared to the synthesized ligands **1–4**.

Ligand exchange reactions with reduced complexes. To a 20 mL round-bottom flask equipped with a magnetic stirrer were charged 0.5 mmol of the copper complex and 0.55 mmol of sodium ascorbate. 10 mL of a mixture of EtOH–H_2O (4 : 1 v/v) was added and the resulting suspension was stirred for 15 min. 0.5 mmol of triazole **I** or **II** was added to the catalyst solution and the reaction was stirred for 16 h at room temperature. The resulting mixture was extracted with DCM, dried over $MgSO_4$ and dried under vacuum. The residue was purified by column chromatography starting with 100% CH_2Cl_2 and gradually increasing the polarity of the eluent by adding MeOH. The purified triazoles were characterized by ^{1}H and compared to the synthesized ligands **1–4**.

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Notes and references

1 See for example: (*a*) W. Keim, in *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley VCH, Germany, 2nd edn, 2004, ch. 1, vol. 1, pp. 15–25; (*b*) J. Yin, Application of Transition Metal Catalysis, in *Drug Discovery and Development: An Industrial Perspective*, ed. M. L. Crawley and B. M. Trost, Wiley, Germany, 1st edn, 2012, ch. 3, vol. 1, pp. 97–163; (*c*) J. Hagen, *Industrial Catalysis: A practical Approach*, Wiley-VCH, Germany, 2nd edn, 2006, ch. 3, vol. 1, pp. 59–80.

2 (*a*) F. Jaouen, E. Proietti, M. Lefevre, R. Chenitz, J.-P. Dodelet, G. Wu, H. T. Chung, C. M. Johnston and P. Zelenay, *Energy Environ. Sci.*, 2011, **4**, 114; (*b*) R. Bashyam and P. Zelenay, *Nature*, 2006, **443**, 63; (*c*) F. Studt, F. Abild-Pedersen, T. Bligaard, R. Z. Sorensen, C. H. Christensen and J. K. Norskov, *Science*, 2011, **320**, 1320; (*d*) G. Wu, K. L. More, C. M. Johnston and P. Zelenay, *Science*, 2011, **332**, 443.

3 (*a*) W. Wang, G. B. Hammond and B. Xu, *J. Am. Chem. Soc.*, 2012, **134**, 5697; (*b*) C. Gunanatan and D. Milstein, *Top. Organomet. Chem.*, 2011, **37**, 55; (*c*) A. Pfaltz and W. J. Dury III, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5723; (*d*) K. Omatsu, M. Ito, T. Kuneida and T. Ooi, *Nat. Chem.*, 2012, **4**, 473; (*e*) J. J. Miller and M. S. Sigman, *J. Am. Chem. Soc.*, 2007, **129**, 2752.

4 (*a*) C. J. ÓBrien, E. A. B. Kantchev, G. A. Chass, N. Hadei, A. C. Hopkinson, M. G. Organ, D. H. Setiadi, T.-H. Tang and D.-C. Fang, *Tetrahedron*, 2005, **61**, 9723; (*b*) P. J. Chirik and K. Weighardt, *Science*, 2010, **327**, 5967; (*c*) R. H. Crabtree, *New J. Chem.*, 2011, **35**, 18; (*d*) G. Chelucci, *Coord. Chem. Rev.*, 2013, **257**, 1887; (*e*) J. Klosin and C. R. Landis, *Acc. Chem. Res.*, 2007, **40**, 1251.

5 (*a*) B. Happ, D. Escudero, M. D. Hager, C. Friebe, A. Winter, H. Görls, E. Altuntas, L. Gonzalez and U. S. Schubert, *J. Org. Chem.*, 2010, **75**, 4025; (*b*) F. Saleem, G. K. Rao, A. Kumar, G. Mukherjee and A. K. Singh, *Organometallics*, 2013, **32**, 3595; (*c*) N. Segaud, J.–N. Rebilly, K. Senechal-David, R. Guillet, L. Billon, J.-P. Baltaze, J. Farjon, O. Reinaud and F. Banse, *Inorg. Chem.*, 2013, **52**, 691; (*d*) J. D. Crowley and E. L. Gavey, *Dalton Trans.*, 2010, **39**, 4035.

6 See for example: (*a*) C. Maeda, S. Yamaguchi, C. Ikeda, H. Shinokubo and A. Osuka, *Org. Lett.*, 2008, **10**, 549; (*b*) K. M. Mullen and M. J. Gunter, *J. Org. Chem.*, 2008, **73**, 3336; (*c*) C. Richardson, C. M. Fitchett, F. R. Keene and P. J. Steel, *Dalton Trans.*, 2008, 2534; (*d*) D. Schweinfurth, K. I. Hardcastle and U. H. F. Bunz, *Chem. Commun.*, 2008, 2203; (*e*) Y. Li, J. C. Huffman and A. H. Flood, *Chem. Commun.*, 2007, 2692; (*f*) T. L. Mindt, H. Struthers, L. Brans, T. Anguelov, C. Scheweinsberg, V. Maes, D. Tourwé and R. Schibli, *J. Am. Chem. Soc.*, 2006, **128**, 15096; (*g*) C. Camp, S. Dorbes, C. Picard and E. Benoist, *Tetrahedron Lett.*, 2008, **49**, 1979; (*h*) T. Ziegler and C. Hermann, *Tetrahedron Lett.*, 2008, **49**, 2166.

7 (*a*) V. V. Rostostev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; (*b*) J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302.

8 (*a*) J. D. Crowley and D. A. McMorran, *Top. Heterocycl. Chem.*, 2012, **28**(31), 84; (*b*) O. Fleishel, N. Wu and

A. Petitjean, *Chem. Commun.*, 2010, **46**, 8454; (*c*) B. M. J. M. Suijkerbuijk, B. N. H. Aerts, H. P. Dijkstra, M. Lutz, A. L. Spek, G. van Koten and R. J. M. Klein Gebbink, *Dalton Trans.*, 2007, 1273.

9 (*a*) P. M. Guha, H. Phan, J. S. Kinyon, W. S. Brotherton, K. Sreenath, J. T. Simmons, Z. Wang, R. J. Clark, N. S. Dalal, M. Shatruk and L. Zhu, *Inorg. Chem.*, 2012, **51**, 3465; (*b*) M. Ostermeier, M.-A. Berlin, R. M. Meudnert, S. Demeshko, F. Meyer, C. Limberg and S. Hecth, *Chem.–Eur. J.*, 2010, **16**, 10202.

10 (*a*) B. Schulze, C. Friebe, S. Hoeppener, G. M. Pavlov, A. Winter, M. D. Hager and U. S. Schubert, *Macromol. Rapid Commun.*, 2012, **33**, 597; (*b*) G. Aromi, L. A. Barrios, O. Robeau and P. Gamez, *Coord. Chem. Rev.*, 2011, **255**, 485; (*c*) A. Noor, J. E. M. Lewis, S. A. Cameron, S. C. Moratti and J. D. Crowley, *Supramol. Chem.*, 2012, **24**, 492; (*d*) J. E. M. Lewis, C. J. McAdam, M. G. Gardiner and J. D. Crowley, *Chem. Commun.*, 2013, **49**, 3398.

11 See for example: (*a*) Y. Chen, W. Yan, N. G. Akhmedov and X. Shi, *Org. Lett.*, 2010, **12**, 344; (*b*) E. Armadio, A. Scrivanti, M. Bortoluzzi, M. Bertoldini, V. Beghetto, U. Matteoli and G. Chessa, *Inorg. Chim. Acta*, 2013, **405**, 188; (*c*) E. Amadio, A. Scrivanti, G. Chessa, U. Matteoli, V. Beghetto, M. Bertoldini, M. Rancan, A. Dolmella, A. Venzo and R. Bertani, *J. Organomet. Chem.*, 2012, **716**, 193; (*d*) D. Schweinfurth, C.-Y. Su, S.-C. Wei, P. Braunstein and B. Sarkar, *Dalton Trans.*, 2012, **41**, 12984; (*e*) D. Canseco-Gonzalez, A. Gniewek, M. Szulmanowicz, H. Mueller-Bunz, A. M. Trzeciak and M. Albrecht, *Chem.–Eur. J.*, 2012, **18**, 6055; (*f*) D. Wang, Y. Zhang, A. Harris, L. N. S. Gautam, Y. Cheng and X. Shi, *Adv. Synth. Catal.*, 2011, **353**, 2584.

12 (*a*) S.-Q. Bai, L. L. Hoh and T. S. A. Hor, *Inorg. Chem.*, 2009, **48**, 1207; (*b*) S.-Q. Bai, L. Yang, J.-L. Zuo and T. S. A. Hor, *Dalton Trans.*, 2013, **42**, 11319; (*c*) X. Han, Z. Weng, D. J. Young, G.-X. Jin and T. S. A. Hor, *Dalton Trans.*, 2014, **43**, 1305.

13 (*a*) L. Yang, Z. Wang, S.-Q. Bai and T. S. A. Hor, *Dalton Trans.*, 2013, **42**, 9437; (*b*) S.-Q. Bai, A. M. Yong, J. J. Hu, D. J. Young, X. Zhang, Y. Zong, J. Xu, J. L. Zuo and T. S. A. Hor, *CrystEngComm*, 2012, **14**, 961; (*c*) J. D. Crowley and P. H. Bandeen, *Dalton Trans.*, 2010, **39**, 612.

14 D. Mendoza-Espinosa, G. E. Negron-Silva, L. Lomas-Romero, A. Gutierrez-Carrillo and D. Soto-Castro, *Synthesis*, 2013, 2431.

15 D. Mendoza-Espinosa, G. E. Negron-Silva, L. Lomas-Romero, A. Gutierrez-Carrillo and R. Santillan, *Synth. Commun.*, 2013, **44**, 807.

16 (*a*) S. V. Voitekhovich, J. V. Filippova, A. G. Sukhanova, A. S. Lyakhov, L. S. Ivashkevish, G. T. Sukhanov and Y. V. Grigoriev, *Inorg. Chem. Commun.*, 2012, **24**, 77; (*b*) G. E. Kostakis, P. Xydias, E. Nordlander and J. C. Plakatouras, *Inorg. Chim. Acta*, 2012, **383**, 327; (*c*) G. F. Manbeck, W. W. Brennessel, W. W. Evans, M. Christopher and R. Eisenberg, *Inorg. Chem.*, 2010, **49**, 2834; (*d*) J. D. Crowley, P. H. Bandeen and L. R. Hanton, *Polyhedron*, 2010, **29**, 70.

17 Data for complex **8**: $C_{32}H_{28}Cl_4CuN_6S_2$; fw 766.06; space group $C2/c$; a = 31.1631(10), b = 13.4153(5), c = 8.5786(3), β = 101.437(3); V = 3515.2(2); Z = 4; d = 1.448 Mg m^{-3}; μ = 1.076 mm^{-1}. Data were collected in an Agilent Gemini Diffractometer using Mo Kα radiation (λ = 0.71073 Å). Data were integrated, scaled, sorted, and averaged using the CrysAlisPro software package. The structures were solved using direct methods, using SHELX 97 and refined by full matrix least squares against F^2. The final refinement parameters R_1 [$I > 2\sigma(I)$] = 0.1664, and wR_2 = 0.4696.

18 G. M. Sheldrick, *SHELXS-97, Program for Crystal Structure Solution and Refinement; Institut Für Anorganishe Chemie*, Göttingen, Germany, 1998.

19 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.

20 *POV RAY, v. 3.5*, Persistence of Vision Raytracer Pty. Ltd, Williamston, Victoria Australia, 2002, retrieved from http://www.povray.org

21 X. Creary, A. Anderson, C. Brophy, F. Crowell and Z. Funk, *J. Org. Chem.*, 2012, **77**, 8756.

22 B. R. Buckley, S. E. Dann and H. Heaney, *Chem.–Eur. J.*, 2010, **16**, 6278.

23 G. E. Negron-Silva, R. Gonzalez-Olvera, D. Angeles-Beltran, N. Maldonado-Carmona, A. Espinoza-Vazquez, M. E. Palomar-Pardave, M. A. Romero-Romo and Rosa Santillan, *Molecules*, 2013, **18**, 4613.

24 H. Lopez-Ruiz, J. E. de la Cerda-Pedro, S. Rojas-Lima, I. Perez-Perez, B. V. Rodriguez-Sanchez, R. Santillan and O. Coreño, *ARKIVOC*, 2013, **iii**, 139.