

Copper(I) complexes bearing carbenes beyond classical NHCs: Synthesis and catalytic activity in “Click Chemistry”

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Abstract. The synthesis and characterization of abnormal *N*-heterocyclic carbene, cyclic (alkyl)(amino)carbene, and mesoionic carbene copper(I) complexes are reported. These organometallic species are obtained *via* a versatile and inexpensive synthetic pathway using readily available reactants, namely copper oxide and iminium salts. The catalytic activity of this series of complexes was evaluated in the [3+2] cycloaddition of alkynes with azides (CuAAC).

Outstanding catalytic properties were observed for the abnormal-NHC and triazolylidene-based copper(I) complexes.

Keywords: copper; abnormal carbene; remote carbene; *N*-heterocyclic carbene; Click chemistry; [3+2] cycloaddition

Introduction

The isolation of a *N*-heterocyclic carbene (NHC, **I**) by Arduengo and co-workers in the early 1990's led to major breakthroughs in organometallic chemistry.^[1] In the course of developing more efficient transition metal based catalytic systems, NHCs have evolved into *workhorses* as ligands for organometallic complexes. The efficiency of these ligands for transition metal catalysts is due to their strong σ -electron donating properties and highly tunable steric features.^[2] In this context, the synthesis of even more electron-donating ligands is a topic of significant interest in the organometallic and homogeneous catalysis communities. During the last decade, the library of stable cyclic carbenes has been enriched by new species such as the abnormal carbenes (*a*NHC, **II**),^[3] cyclic (alkyl)(amino)carbenes (CAAC, **III**),^[4] mesoionic carbenes (MIC, **IV**),^[5] and bis(amino)cyclopropenylidenes (BAC, **V**),^[6] all of them being more electron-donating than NHCs (Figure 1).^[7,8,9,10]

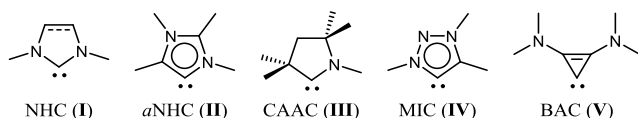
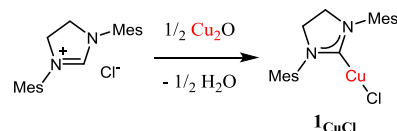


Figure 1. Carbenes considered as ligands in this work.

It has already been shown that in certain instances metal complexes supported by these novel types of carbene (**II-IV**) outperform their NHC (**I**) counterparts in catalysis.^[8a,11] So far, reports on copper complexes bearing such ligands are scarce^[12,13] and have mainly focused on triazol-5-ylidene (**IV**) derivatives.^[14] This might be explained by the fact that all reported synthetic methodologies involve the highly reactive and air- and moisture-sensitive free carbene species. In contrast, NHC-Cu(I) complexes are readily accessible,^[1e-i,15,16] as shown by the versatile, *green* and cost/user-friendly synthetic strategy as demonstrated with **1**_{CuCl} (Scheme 1).^[17]

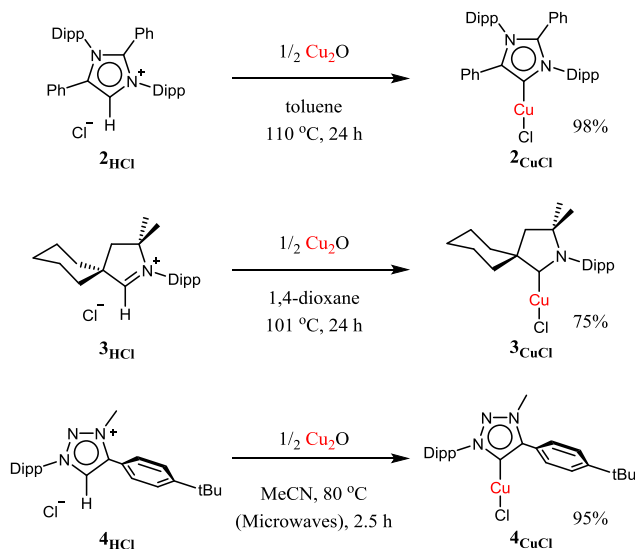


Scheme 1. Synthesis of [Cu(Cl)(SIMes)] **1**_{CuCl} (Mes = mesityl).

Herein, we report the generalization of this approach to the preparation of *a*NHC-, CAAC- and MIC-Cu(I) complexes. The catalytic activity of these complexes was evaluated in the [3+2] cycloaddition of alkynes and azides (CuAAC).^[18]

Results and Discussion

We began our study with the metallation of the C²-substituted imidazolium salt **2**_{HCl}, which is the classical precursor of free *a*NHC **II**.^[3] When **2**_{HCl} was reacted with copper oxide in refluxing toluene for 24 hours, a clean reaction was observed (Scheme 2). Interestingly **2**_{CuCl} was obtained in analytically pure form in 98% yield after simple filtration through Celite and removal of the volatiles *in vacuo*. This protocol represents a dramatic improvement over the previously reported procedure by Mandal and co-workers using the free *a*NHC **II**.^[12]



Scheme 2. Synthesis of complexes **2**_{CuCl}, **3**_{CuCl} and **4**_{CuCl} (Dipp = 2,6-(Diisopropyl)phenyl).

Similarly, **3**_{CuCl} was prepared from the corresponding cyclic iminium **3**_{HCl} and copper oxide in refluxing 1,4-dioxane for 24 hours (Scheme 2). After workup and recrystallization from dichloromethane/pentane, **3**_{CuCl} was obtained in 75% yield.

Conventional heating conditions used for the preparation of **2**_{CuCl} and **3**_{CuCl} did not result in full conversion of **4**_{HCl} even after 24 hours in refluxing solvents. However, under microwave irradiation^[19] for 2.5 hours at 80 °C in acetonitrile, the copper complex **4**_{CuCl}, bearing a 1,2,3-triazol-5-ylidene **IV**, was cleanly obtained. After recrystallization from dichloromethane/diethyl ether, **4**_{CuCl} was isolated in a 95% yield.

Noteworthy, this synthetic approach necessitates the use of chloride salts, which are not always readily accessible for non-classical NHCs. However it was possible, for all the ligands investigated in this study, to exchange the BF₄ anion for Cl⁻ using Amberlite 402 IRA Cl-resin.

The atom connectivity in copper complexes **2**_{CuCl}, **3**_{CuCl}, and **4**_{CuCl} was unambiguously established by single crystal X-ray diffraction studies (Figure 2). All complexes adopt a slightly distorted linear geometry

with Cl-Cu-Cl angles between 173.53(17)° and 174.84(14)° (Table 1). The Cu-C1 bond lengths are shorter [1.871(7)-1.895(6) Å] than those found in the corresponding unsaturated NHC complexes, such as [Cu(Cl)(IMes)] and [Cu(Cl)(IPr)]^[20] [1.956(10) Å and 1.953(8) Å, respectively]; however these bond distances are similar to those observed for saturated NHCs such as in [Cu(Cl)(SIPr)] [1.896(7) Å].^[16a,20, 21]

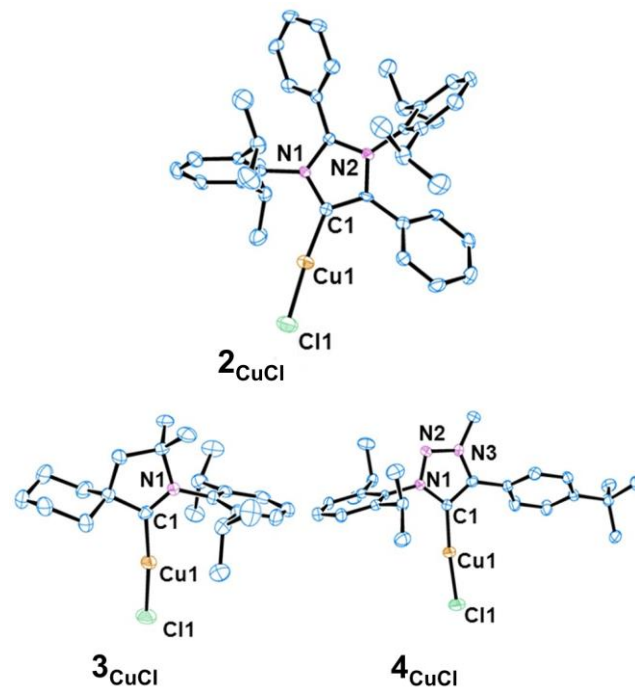


Figure 2. Molecular representations of *a*NHC, CAAC, MIC copper(I) complexes **2**_{CuCl}, **3**_{CuCl}, and **4**_{CuCl}, respectively. Hydrogen atoms are omitted for clarity.^[22]

The steric hindrance of these ligands was assessed using the SambVca application (Table 1).^[23] [Cu(Cl)(*a*NHC)] **2**_{CuCl} possesses a moderately congested metal centre (% *V*_{Bur} = 40.5) despite the presence of the bulky 2,6-(diisopropyl)phenyl *N*-substituent. The CAAC ligand in **3**_{CuCl} is the more sterically demanding of this series with a % *V*_{Bur} of 44.8. However, it remains a relatively small ancillary ligand compared to the commonly used [Cu(Cl)(IPr)] (% *V*_{Bur} = 49.6).^[21a,24] Surprisingly, the triazolylidene ligand in **4**_{CuCl} is significantly smaller (% *V*_{Bur} = 33.3). Noteworthy, because of the dissymmetric environment around the carbene center in **2**_{CuCl}-**4**_{CuCl}, these complexes feature both a heavily congested and a more accessible quadrant, which may very well induce particularly interesting behavior in catalysis.^[25]

Table 1. % *V*_{Bur} and selected bond lengths (Å) and angles (°) (esd) for complexes **2**_{CuCl}-**4**_{CuCl}.

Complex	2 _{CuCl}	3 _{CuCl}	4 _{CuCl}
% <i>V</i> _{Bur} ^{a)}	40.5	44.8	33.3
Cu-C	1.871 (7)	1.895 (6)	1.876 (4)
Cl-Cu-C	173.53 (17)	174.18 (17)	174.84 (14)

a) Calculated with Cu-C = 1.9 Å.

The catalytic activity of complexes **2**_{CuCl}-**4**_{CuCl} was studied for the [3+2] cycloaddition of azides with alkynes (CuAAC), which represents the flagship transformation of “Click Chemistry”.^[26] The results are compared with those obtained with the [Cu(Cl)(SImes)] **1**_{CuCl},^[15a,26b,27] and the recently reported [Cu(Cl)(BAC)] **5**_{CuCl} (Figure 3).^[28] Three different substrate sets were chosen. The reactions were conducted at room temperature, without solvent, and using 0.5 mol% of catalyst loading. The kinetic profile of these reactions was monitored by gas chromatography (Figure 4).

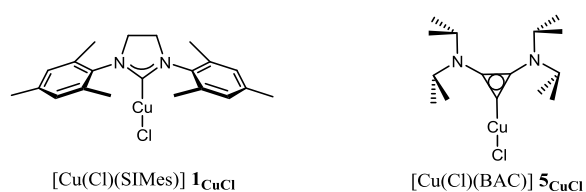


Figure 3. Previously reported [Cu(Cl)(SImes)] **1**_{CuCl} and [Cu(Cl)(BAC)] **5**_{CuCl}.

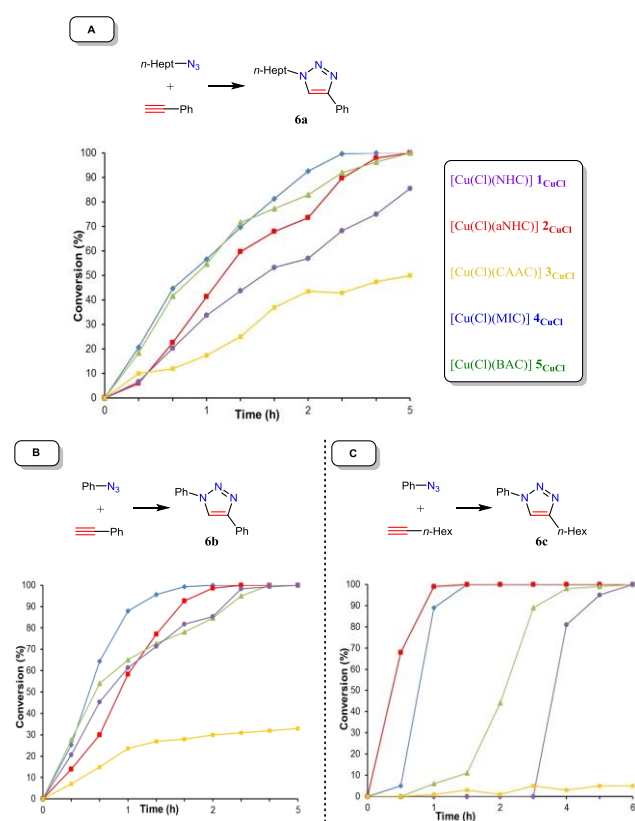
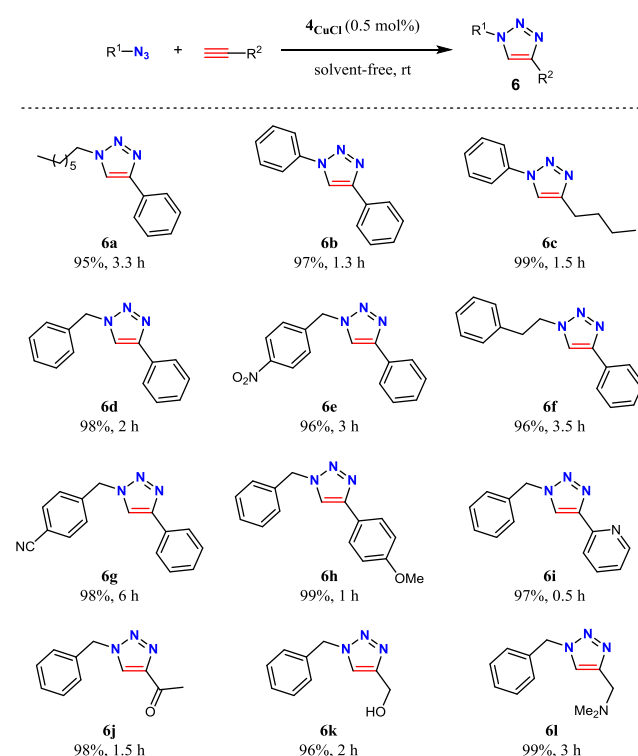


Figure 4. Kinetic profiles of the [3+2] cycloaddition reactions catalyzed by complexes **1-5**_{CuCl} (lines are visual aids and not curve fits). Reaction conditions: Catalyst (0.5 mol%), azide (1.0 mmol), alkyne (1.1 mmol), 25 °C, solvent-free.

For the three sets of substrates, excellent conversions were observed within 5 hours with all catalysts, except with [Cu(Cl)(CAAC)] **3**_{CuCl} (maximum conversion: 48%). In all cases, *a*NHC, MIC and BAC copper complexes **2**_{CuCl}, **4**_{CuCl} and **5**_{CuCl}, respectively, are activated much faster than the classical NHC analogue **1**_{CuCl}. The most challenging reaction, phenylazide with 1-hexyne, allows a better discrimination of the catalysts. The *a*NHC and MIC complexes **2**_{CuCl} and **4**_{CuCl} clearly outperform the BAC analogue **5**_{CuCl}; 50% conversion are observed after 0.3, 0.6, and 2.1 hours, respectively; note that this conversion is reached only after 4.0 hours with the NHC complex **1**_{CuCl}. The main difference lies in the duration of the initiation period, **2**_{CuCl} < **4**_{CuCl} << **5**_{CuCl} << **1**_{CuCl}.

Since the *a*NHC and MIC complexes **2**_{CuCl} and **4**_{CuCl} performed almost equally well, the latter was chosen to study the scope of the reaction, because of its easier preparation. Using the same experimental conditions as above, a series of six azides and seven terminal alkynes were tested, and the reactions were monitored to assess the time required to reach completion (Scheme 3).



Scheme 3. Scope of the [3+2] cycloaddition of azides and alkynes promoted by complex **4**_{CuCl}. Reaction conditions: azide (1.0 mmol), alkyne (1.1 mmol), **4**_{CuCl} (0.5 mol%), 25 °C, solvent-free. Isolated yields are given, average of two reactions.

The reactions reached completion within 0.5 to 6 hours with isolated yields ranging from 95 to 99%. As expected, the range of functionalities tolerated is broad and includes nitro (**6e**), nitriles (**6g**), ethers (**6h**),

carbonyls (**6j**), alcohols (**6k**) and amines (**6l**) functional groups. The slowest reaction was observed for the formation of triazole **6g**, possibly because the metal interacting with the cyano group, which is away from the azide moiety. However, even with this difficult substrate, **6g** is quantitatively formed within 6 hours, showcasing the efficiency of the [Cu(Cl)(MIC)] **4**_{CuCl}. At the other extreme, when 2-ethynylpyridine is used, heterocycle **6i** was obtained quantitatively in *only 30 minutes!* In this case, and in contrast with the cyano derivative, the pyridine might template the metal close to the reaction center.

Conclusion

In summary, we generalized the use of Cu₂O for the preparation of a series of copper(I) chloride complexes, featuring strongly basic carbenes. This methodology circumvents the preparation of highly air-sensitive free carbenes. [Cu(Cl)(aNHC)] **2**_{CuCl} and [Cu(Cl)(MIC)] **4**_{CuCl} complexes were activated significantly faster than their NHC analogues, when promoting [3+2] cycloadditions of a variety of azides with alkynes. Further investigations into the catalytic potential of this series of copper complexes are currently under investigation in our laboratories.

Experimental Section

General considerations

All reactions were performed under inert atmosphere using standard Schlenk and glovebox techniques unless stated otherwise. Solvents were dispensed from a solvent purification system. All other reagents were used without further purification. Microwave-assisted reactions were carried out in a CEM Discover microwave. ¹H, ¹⁹F-¹H and ¹³C-¹H Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AVANCE 300 or a Bruker AVANCE 400 Ultrashield spectrometer using the residual solvent peak as reference^[29] (CDCl₃: δ_H = 7.26 ppm, δ_C = 77.16 ppm; C₆D₆, δ_H = 7.16 ppm, δ_C = 128.06 ppm and CD₃CN, δ_H = 1.94 ppm, δ_C = 1.32 and 118.26 ppm) at 298K. Gas chromatography (GC) analyses were performed on an Agilent 7890A apparatus equipped with a flame ionization detector and a (5%-Phenyl)-methylpolysiloxane column (30 m, 320 μm, film: 0.25 μm).

Synthesis of **2**_{CuCl}, **3**_{CuCl} and **4**_{CuCl}

In a glovebox, a vial was charged with the ligand salt, Cu₂O (0.65 equiv.) and the appropriate volume of solvent. The reaction mixture was stirred during the given time period at the indicated temperature (either under microwave or thermal heating). The reaction mixture was filtered through a pad of Celite and all volatiles were removed *in vacuo*. The residue was dissolved in CH₂Cl₂ (1mL) and Et₂O (10 mL) was added. The product was collected by filtration and washed with Et₂O (2x10 mL).

Chloro[1,3-bis(2,6-diisopropylphenyl)-2,4-diphenylimidazol-5-ylidene]copper(I), **2**_{CuCl}. Yellow/green solid (398 mg, 98%). ¹H NMR (300 MHz, CDCl₃, 298K, TMS): δ (ppm) = 7.50-7.40 (m, 5H, CH_{Ar}), 7.22-7.16 (m, 7H, CH_{Ar}), 7.06 (t, ³J(H,H) = 8.3 Hz, 2H, CH_{Ar}), 6.88-6.85 (m, 2H, CH_{Ar}), 2.72-2.53 (m, 4H, CH-CH₃), 1.43 (d, ³J(H,H) = 6.8 Hz, 6H, CH₃), 0.96 (d, ³J(H,H) = 6.8 Hz, 6H, CH₃), 0.82 (overlapped d, ³J(H,H) = 6.8 Hz, 6H, CH₃), 0.80 (overlapped d, ³J(H,H) = 6.8 Hz, 6H, CH₃). ¹³C-¹H NMR (75 MHz, CDCl₃, 298K, TMS): δ (ppm) = 159.5 (C-Cu), 145.0 (C^{IV}), 144.6 (C^{IV}), 144.4 (C^{IV}), 141.7 (C^{IV}), 135.8 (C^{IV}), 131.1 (CH_{Ar}), 131.0 (CH_{Ar}), 130.6 (CH_{Ar}), 130.5 (CH_{Ar}), 130.4 (C^{IV}), 129.5 (CH_{Ar}), 129.0 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.0 (CH_{Ar}), 125.3 (CH_{Ar}), 124.6 (C^{IV}), 123.7 (C^{IV}), 28.9 (CH-CH₃), 28.6 (CH-CH₃), 25.9 (CH₃), 23.7 (CH₃), 23.5 (CH₃), 22.6 (CH₃). **Elemental analysis calcd (%) for C₃₉H₄₄ClCuN₂** : C 73.22, H 6.93, N 4.38; found: C 73.15, H 7.02, N 4.45.

Chloro[2-(2,6-diisopropylphenyl)-3,3-(dimethyl)-2-azaspiro[4.5]dec-1-ylidene]copper(I), **3**_{CuCl}. Pale pink solid (220 mg, 75%). ¹H NMR (300 MHz, C₆D₆, 298K): δ (ppm) = 7.16-7.09 (m, 1H, CH_{Ar}), 7.00-6.98 (m, 2H, CH_{Ar}), 2.66 (septet, ³J(H,H) = 6.8 Hz, 2H, CH-CH₃), 2.00-1.94 (m, 2H, H₂C_{Cy}), 1.57-1.54 (m, 2H, H₂C_{Cy}), 1.41 (d, ³J(H,H) = 6.8 Hz, 6H, CH₃-CH), 1.38 (s, 2H, CH₂), 1.13-1.00 (m, 12H, H₂C_{Cy} and CH₃-CH), 0.78 (s, 6H, C(CH₃)₂). ¹³C-¹H NMR (75 MHz, C₆D₆, 298K): δ (ppm) = 249.9 (C-Cu), 145.3 (C^{IV}), 134.6 (C^{IV}), 130.1 (CH_{Ar}), 124.9 (CH_{Ar}), 79.8 (C^{IV}), 59.2 (C^{IV}), 45.7 (CH₂), 36.0 (H₂C_{Cy}), 29.3 (CH-CH₃), 29.1 (CH₃), 27.2 (CH₃-CH), 25.2 (H₂C_{Cy}), 22.5 (H₂C_{Cy}), 22.2 (CH₃-CH). **Elemental analysis calcd (%) for C₂₃H₃₅ClCuN**: C 65.07, H 8.31, N 3.30; found: C 64.93, H 8.35, N 3.39.

Chloro[1-(2,6-diisopropylphenyl)-3-(methyl)-4-(4-tert-butylphenyl)-1,2,3-triazol-5-ylidene] copper(I) **4**_{CuCl}. Colorless solid (438 mg, 95%). ¹H NMR (400 MHz, CDCl₃, 298K, TMS): δ (ppm) = 7.69 (d, ³J(H,H) = 8.4 Hz, 2H, CH_{Ar}), 7.56 (d, ³J(H,H) = 8.4 Hz, 2H, CH_{Ar}), 7.52 (t, ³J(H,H) = 8.1 Hz, 1H, CH_{Ar}), 7.30 (d, ³J(H,H) = 8.1 Hz, 2H, CH_{Ar}), 4.24 (s, 3H, N-CH₃), 2.31 (septet, ³J(H,H) = 6.8 Hz, 2H, CH-CH₃), 1.37 (s, 9H, CH₃), 1.30 (d, ³J(H,H) = 6.8 Hz, 6H, CH₃-CH), 1.16 (d, ³J(H,H) = 6.8 Hz, 6H, CH₃-CH). ¹³C-¹H NMR (101 MHz, CDCl₃, 298K, TMS): δ (ppm) = 166.4 (Cu-C_{triazolylidene}), 153.6 (C^{IV}), 148.6 (C^{IV}), 144.9 (C^{IV}), 135.7 (C^{IV}), 131.1 (CH_{Ar}), 129.2 (CH_{Ar}), 126.5 (CH_{Ar}), 124.1 (CH_{Ar}), 123.9 (C^{IV}), 37.7 (N-CH₃), 34.9 (C^{IV}), 31.2 (CH-CH₃), 28.6 (CH₃), 24.3 (CH₃-CH), 24.2 (CH₃-CH). **Elemental analysis calcd (%) for C₂₅H₃₃ClCuN₃** : C 63.27, H 7.01, N 8.85; found: C 63.15, H 7.16, N 8.72.

General procedure for catalysis.

A vial was charged with the azide (1.00 mmol), alkyne (1.10 mmol) and the appropriate catalyst (0.5 mol%). The reaction mixture was stirred at 25 °C for the appropriate amount of time in solvent-free conditions. The conversion was monitored by GC analysis.

Supporting Information.

Synthesis and characterization of ligands and copper complexes $2_{\text{CuCl}}-4_{\text{CuCl}}$, 3D mapping and calculations of % V_{Bur} , synthesis and characterization of substrates and triazoles (**6**), general procedures for catalysis, ^1H and $^{13}\text{C}\{-^1\text{H}\}$ NMR spectra of all ligands, complexes, substrates and catalysis products.

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