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Mechanistic Study in Azide-Alkyne Cycloaddition (CuAAC) Catalyzed by Bifunctional Trinuclear Copper(I) Pyrazolate Complex: Shift in Rate-Determining Step

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In memory of Professor Rolf Huisgen.

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Abstract

Trinuclear copper(I) pyrazolate $[Cu(3,5\text{-}(CF_3)_2Pz)]_3$ was employed in a mechanistic study of azide-alkyne cycloaddition (CuAAC). It was shown that the copper complex operates as a bifunctional catalytic system (copper source and Brønsted base) under mild conditions (RT and air atmosphere) at low catalyst loading (1 mol%). The rate-determining step of the reaction is the first C-N bond formation between azide and acetylene (azide migratory insertion) but not the copper(I) acetylide formation as commonly assumed. It was supported by the observed kinetic

isotope effect equaling 1.1 and by DFT calculations. The reaction has a second-order dependence on the catalyst concentration implicating the two copper(I) centers participate in the metallacycle formation step from "bis-butterfly" tetranuclear complex $Cu_4L_4(RC{\equiv}CH)_2$ in the rate-determining step. DFT calculations proved that the pyrazolate ligand acts as a Brønsted base and deprotonates the acetylene molecule providing successful catalysis. A plausible catalytic cycle of the reaction has generated based on DFT calculations.

Keywords:

Click reaction, azide-alkyne cycloaddition, copper(I) pyrazolate, kinetic isotope effect, DFT calculations, Brønsted base catalysis

1. Introduction

Macrocyclic copper(I) pyrazolates constitute an attractive class of coordination compounds able to form supramolecular aggregates *via* metalophilic or acid-base interactions,[1,2] as well as exhibit bright photoluminescence.[3] However, despite the widespread use of the copper(I) pyrazolates in coordination and supramolecular chemistry, their potential is still not fully disclosed. Obviously, such complexes, having the metal ion in the system, can catalyze various organic transformations. Being the Lewis acids, the copper centers of trinuclear pyrazolate complexes can activate the substrates *via* intermolecular acid/base interactions providing the valuable target products. Meanwhile, the field has great unexplored potential for the catalysis. To best of our knowledge, only several reports about the application of the trinuclear copper (I) and (II) pyrazolate complexes as catalysts have been reported so far including our recent work.[4-6] In 2009, Pombeiro et al. have reported the peroxidative oxidation of cycloalkanes catalyzed by the trinuclear copper(II) pyrazolate derivatives.[4a] The valuable cyclic alcohols and ketones were isolated with overall yields of up to 34% and TONs up to 42.[4a] In 2017, Li and co-workers have synthesized multicomponent copper(I) metal-organic frameworks based on 4-pyrazole carboxylic acid and applied these complexes as catalysts in the oxidation of CO and aromatic alcohols and the decomposition of hydrogen peroxide (H_2O_2).[4b] In 2019, Dias and co-workers applied a copper complex $[Cu(3,5\text{-}(CF_3)_2Pz)]_3$ as a precatalyst for the alkyne $C_{(sp)}$-H bond carboxylation with CO_2, azide-alkyne cycloaddition reaction and thiol addition to phenylacetylene affording vinyl sulfides.[6] Also, there are two examples of the application of polynuclear copper complexes based on pyrazolates as catalysts in literature.[7] For example, Maspero and co-workers have used the homoleptic tetrameric $[Cu(dcsbpz)]_4$ (dcsbpz = 3,5-dicarbo-sec-butoxy pyrazole) and $[Cu(dtbpz)]_4$ (dtbpzas = 3,5-di-*tert*-butyl pyrazole) copper(I) pyrazolate derivatives as catalysts for the cyclopropanation of alkenes with ethyl diazoacetate with favored formation of the *trans*-diastereoisomeric products.[7a] Lang and co-workers have used the polynuclear copper(II) pyrazolate complex based on 1*H*-pyrazole-3,5-dicarboxylic acid dimethyl ester as a catalyst in the

condensation of nitriles with 2-amino alcohols to produce various 2-oxazolines with up to 90% yields.[7b] In another work, Martins and Guedes da Silva et al. reported the application of copper(I) C-scorpionate complexes based on pyrazolates for catalysis of azide-alkyne cycloaddition in an aqueous media, however, a high temperature (125 °C) and microwave irradiation were required in this case.[8]

In 2002, there was a report about the synthesis of alkyne copper complex Cu_2(μ-[3,5-$(CF_3)_2$Pz])$_2$($Me_3SiC{\equiv}CSiMe_3$)$_2$ as a chemical vapor deposition precursor of copper.[9] Recently, we and Dias group independently have shown that the acetylenes can coordinate to a trinuclear copper(I) pyrazolate complex **[CuL]$_3$** (L = 3,5-$(CF_3)_2$Pz) *via* π-coordination of a carbon-carbon triple bond to copper centers forming polynuclear complexes **A, B** or **C** correspondingly.[5,6,10] There was no copper(I) acetylide formation during the interaction in contrast to literature reports[11] as was proved by NMR-, IR-spectroscopy investigations, and by a single crystal X-Ray analysis (Figure 1).[5,6]

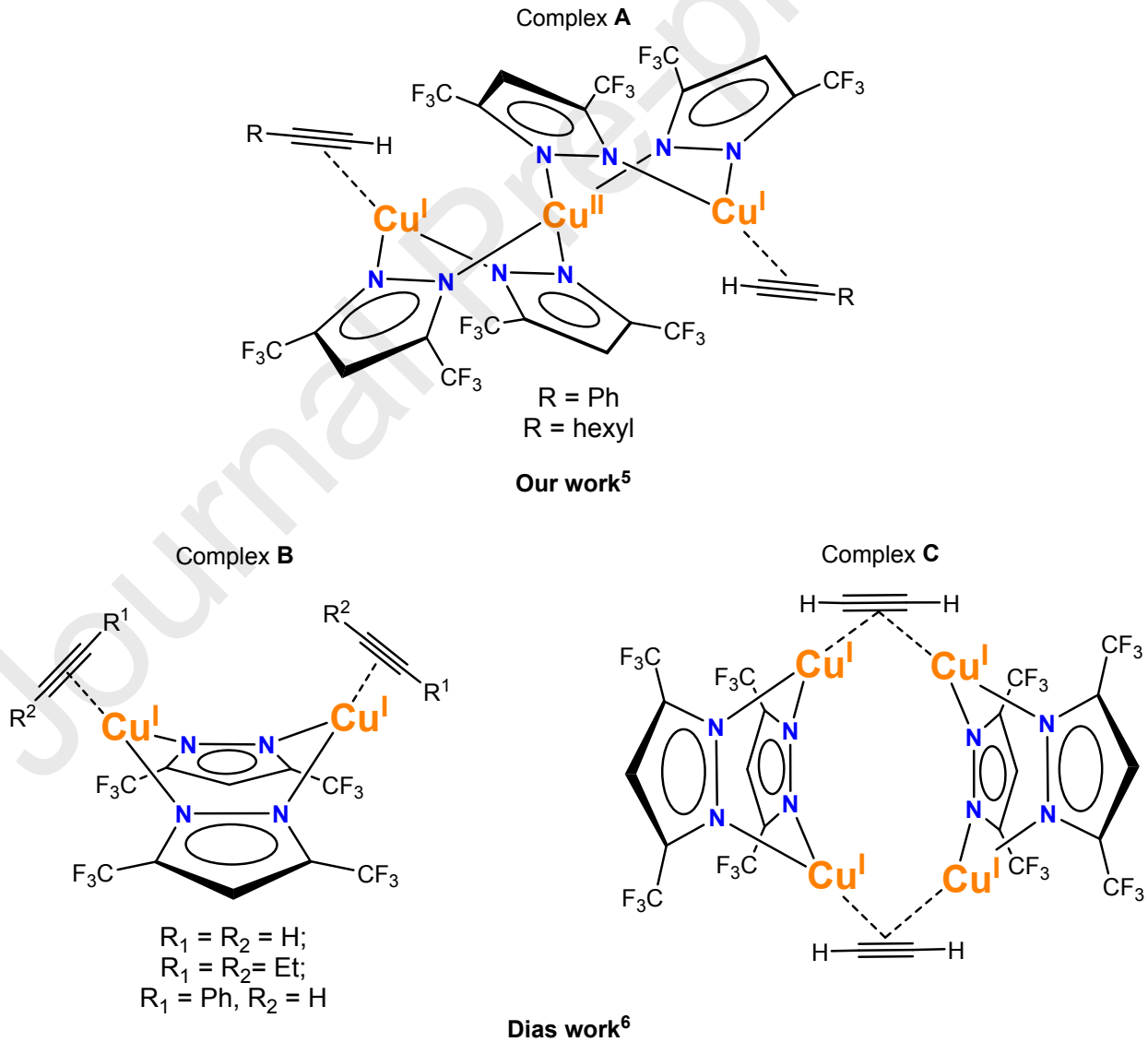
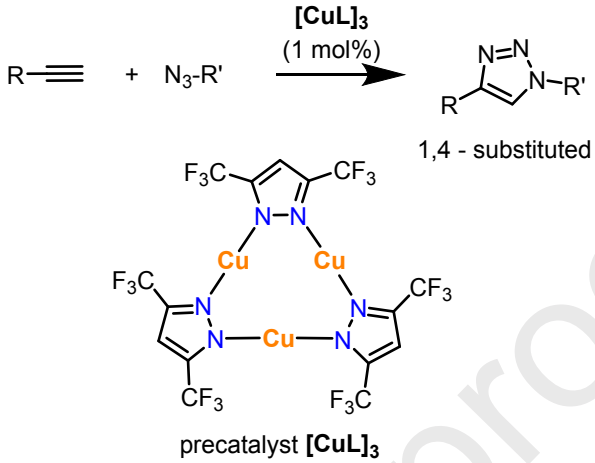


Figure 1. Chemical structures of the copper pyrazolate adducts with terminal alkynes.

Despite the importance of copper in chemistry and the availability of a wide scope of copper(I) pyrazolates,[1-3] their use as catalysts in alkyne transformations remain virtually unexplored. As proof-of-principle, we quite recently demonstrated that the trinuclear copper(I) pyrazolate complex **[CuL]$_3$** efficiently catalyzes the alkyne-azide cycloaddition (CuAAC) ("Click reaction")[12,13] of phenylacetylene and 1-octyne with *ortho*-fluorobenzyl azide (Scheme 1).[5]



Scheme 1. 1,2,3-triazole syntheses *via* "click reaction".

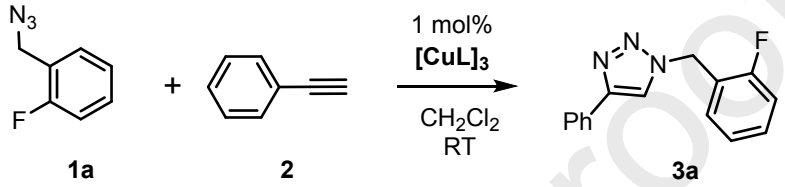
As known, the resulting 1,4-substituted 1,2,3-triazoles have a broad interest in modern pharmaceuticals.[14,15] Moreover, CuAAC is a simple and powerful tool to conjugate molecular pieces together, for instance, in applications of bioconjugation,[15e] surface modification,[16] and syntheses of new polymeric materials,[17] for construction and modification of MOFs[18], and etc. To date, a lot of copper(I) catalysts were applied for the CuAAC,[11-13] however, in many cases, the harsh conditions (polar solvents, high temperatures, extra base, and etc.) are required.[13d,13g,19,20] Although the mechanism of this reaction is well-known and studied,[13g,13h,19,20] there is still going disputation about the mechanistic aspect depending on the catalytic system and substrate class. Commonly, based on works by Finn and Fokin,[13d] and Zhu,[13g,20d] acetylide formation is the rate-determining step (RDS) of the CuAAC reaction. On another hand, recently, Seath et al. observed the shift of RDS from acetylide formation to azide ligation/migratory insertion depending on the structure of substrates.[21]

With these precedents in hand, we aimed to partially fill this knowledge gap. Herein, we report the detailed mechanistic study of CuAAC reaction catalyzed by the trinuclear copper(I) pyrazolate complex **[CuL]$_3$** (Scheme 1). Experimentally with theoretical insights (DFT calculations), it was shown that the copper(I) complex operates as a bifunctional catalytic system (Scheme 1). Moreover, the rate-determining step is the first C-N bond formation between azide and acetylene (azide migratory insertion) in contrast to the commonly assumed copper(I) acetylide formation.[13d,20b,20d] Our finding nicely complements the recent observation by Burley and Watson where an alkyne-specific shift in an RDS was evidenced.[21]

2. Results and discussion

The study was started by the investigating of the azide-alkyne cycloaddition reaction of *ortho*-fluorobenzyl azide **1a** with phenylacetylene **2** catalyzed by the trinuclear copper(I) pyrazolate **[CuL]$_3$** (Table 1). The click reaction conducted in CH_2Cl_2 in the presence of 1 mol% copper complex at room temperature under air after 4 hours furnished 1,4-substituted 1,2,3-triazole **3a** in >99% conversion (Table 1, entry 1). Importantly, in each experiment no formation of any side products, even Glaser coupling products,[22] was observed. Next, the solvent effect was studied (Table 1, entries 2-8).

Table 1. Reaction conditions screening for CuAAC.[a]



entry	change from the "*standard conditions*"	time (h)	convn (%)[b]
1	None	4	>99
2	hexane as the solvent	4	89
3	toluene as the solvent	4	76
4	1,2-dichloroethane as the solvent	4	99
5	MeCN as the solvent	4	96
6	THF as the solvent	4	68
7	MeOH as the solvent	4	21
8	water as the solvent	4	94
9	no solvent	4	>99
10	3 mol% of CuI instead of **[CuL]$_3$**	24	NR
11	3 mol% of CuI and 3 mol% of 3,5-$(CF_3)_2$Pz instead of **[CuL]$_3$**	24	NR
12	3 mol% $[Cu(MeCN)_4]BF_4$ instead of **[CuL]$_3$**	24	traces

[a]Reaction conditions: *ortho*-fluorobenzyl azide **1a** (0.35 mmol), phenylacetylene **2** (0.35 mmol, 1 equiv.) and **[CuL]$_3$** (1 mol%, 3.5 μmol) were stirred in CH_2Cl_2 (1 mL) (or another solvent) at room temperature under air at indicated time. [b]Determined by ^{1}H NMR. L = 3,5-bis(trifluoromethyl)pyrazolate. NR = no reaction.

The conversions in aprotic non-polar organic solvents such as hexane and toluene were slightly decreased (89% and 76%, correspondingly) (Table 1, entries 2,3). More polar aprotic solvents 1,2-dichloroethane and MeCN gave excellent conversions after 4 h (Table 1, entries 4,5). The conversion was lower in THF (67%) (Table 1, entry 6). Expectedly, the protic solvent MeOH was a too polar reaction media with low conversion (21%) (Table 1, entry 7). Water was also a good

tolerant solvent giving the desired product with 94% conversion (Table 1, entry 8). The reaction conducted in neat *ortho*-fluorobenzyl azide **1a** and phenylacetylene **2** without any solvent also gave the 1,4-substituted 1,2,3-triazole **3a** in >99% conversion (Table 1, entry 9).

Furthermore, the control experiments showed that no target product **3a** was formed when either 3 mol% of CuI or a combination of 3 mol% CuI and 3,5-bis(trifluoromethyl)pyrazole were used as catalysts (Table 1, entries 10,11). $[Cu(MeCN)_4]BF_4$ (3 mol %) gave only a trace amount of the desired product **3a** under optimized conditions (Table 1, entry 12).

2.1 Mechanistic study

Next, we performed a set of experiments, kinetic studies, and measurements for the mechanistic investigation of the azide-alkyne cycloaddition reaction catalyzed by **$[CuL]_3$** with the involvement of DFT calculations.

As was already mentioned above, we evidenced the direct interaction of copper(I) pyrazolate with the triple bond of phenylacetylene **2** *via* η^2-coordination and no copper(I) acetylide complex formation by NMR and IR spectroscopies in our previous work.[5] Furthermore, there were no any feasible interactions of azide with a complex **$[CuL]_3$** in CH_2Cl_2.[5]

To determine what type of copper-pyrazolate particles are in the solution, the system was investigated at a molecular level by using electrospray ionization mass spectrometry (ESI-MS). Mass spectrum of the copper(I) complex **$[CuL]_3$** measured in MeCN in a negative mode at concentration 10^{-4} mg/mL clearly showed the presence of several metal complex species: $[CuL_2]^-$ at m/z 468.9405, $[Cu_2L_3]^-$ at m/z 734.8749, $[Cu_3L_4]^-$ at m/z 1002.8086 and $[Cu_5Pz_6]^-$ at m/z 1534.6836 (see Fig. S1, S3 in SI). On the other hand, the mass spectrum of copper(I) complex measured in MeCN in a positive mode showed the presence of $[Cu_2L(MeCN)_2]^+$ at m/z 410.9158 and $[Cu_3L_2(MeCN)_2]^+$at m/z 678.8485 (see Fig. S2, S3 in SI). Unfortunately, we didn't detect any alkyne bounded metal complex species in solution when we conducted the experiments with the addition of phenylacetylene **2** to the solution of **$[CuL]_3$** in MeCN. Probably, the reason is the weak interaction between copper species and alkyne **2** that was not enough stable under ESI-MS conditions. The addition of 1 equiv. of azide **1d** didn't affect the ratio of the copper ions confirming there is no interaction between azide and the copper complex **$[CuL]_3$** in solution. Notably, the oxidation of detected $[Cu_3L_4]^-$ ion at m/z 1002.8086 in the presence of oxygen and following by the coordination with phenylacetylene **2** gave the complex **A** [5] (the central copper ion has +2 charge in Fig. 1). From another hand, recently Dias and co-workers described the crystal structure of the di-nuclear complex **B** ($Cu_2(\mu$-[3,5-$(CF_3)_2$Pz])$_2$(HC≡CPh)$_2$) (see Fig. 1),[6] which are formed either after dissociation of **$[CuL]_3$** in solution in the presence of alkyne or after the reorganization of the copper complex **A**.

To ascertain the number of the catalyst molecules in the transition state of the reaction, the order with respect to the substrates and catalyst had to be quantified. For this purpose, the reactions were carried out at different concentrations of each substrate/component whilst keeping the other component concentration constant and monitored by IR spectroscopy. The initial zero order rates of the reactions were determined and the coefficients x and y in **equation 1** were found to be 1.16 and 0.54 respectively (see Fig. S5 and S7 in SI). Thus, *ortho*-fluorobenzyl azide **1a** shows a first-order behavior that means one molecule of the substrate entered the rate limiting stage of the reaction (see Fig. S5 in SI). Phenylacetylene **2**, in excess amounts, has fractional order (0.54), suggesting that two molecules of alkyne participate in the transition state and only one of them reacts (see Fig. S7 in SI) (see also DFT calculations, *vide infra*). The reaction is second-order in copper pyrazolate **[CuL]$_3$** (z = 1.9) when it is maintained at catalytic levels (<5 mol %, Figure 2). A second-order dependence on copper is consistent with the commonly accepted kinetic model, which favors the participation of two copper(I) centers in the metallacycle formation step based on both kinetic data[13d,20b] and computations.[23] Furthermore, our experimental data have been proved by DFT calculations (see *vide infra*).

$$V = \frac{[\mathbf{3a}]}{dt\,[\mathbf{3a}]_0} = k\,[\mathbf{1a}]^x\,[\mathbf{2}]^y\,[[\mathbf{CuL}]_3]^z \qquad \textbf{(eq 1)}$$

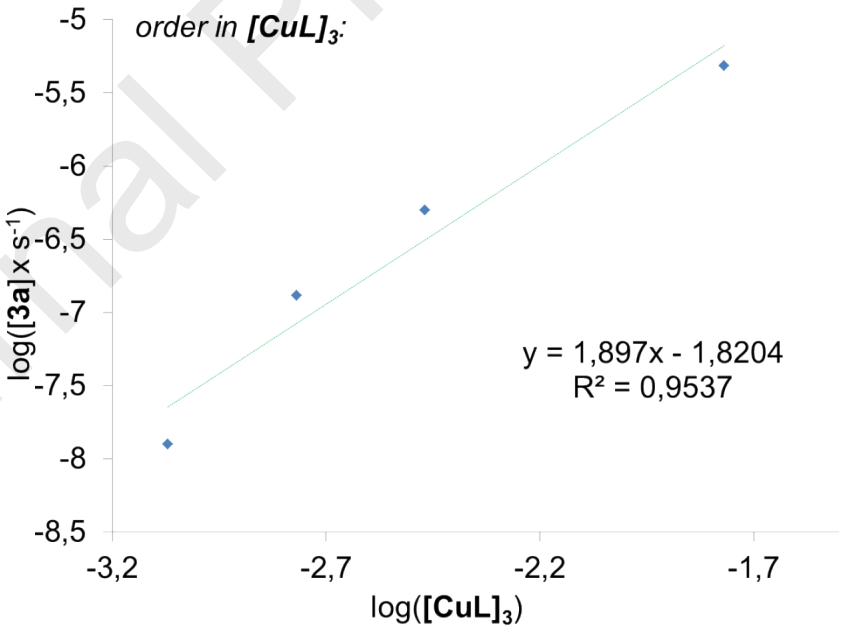
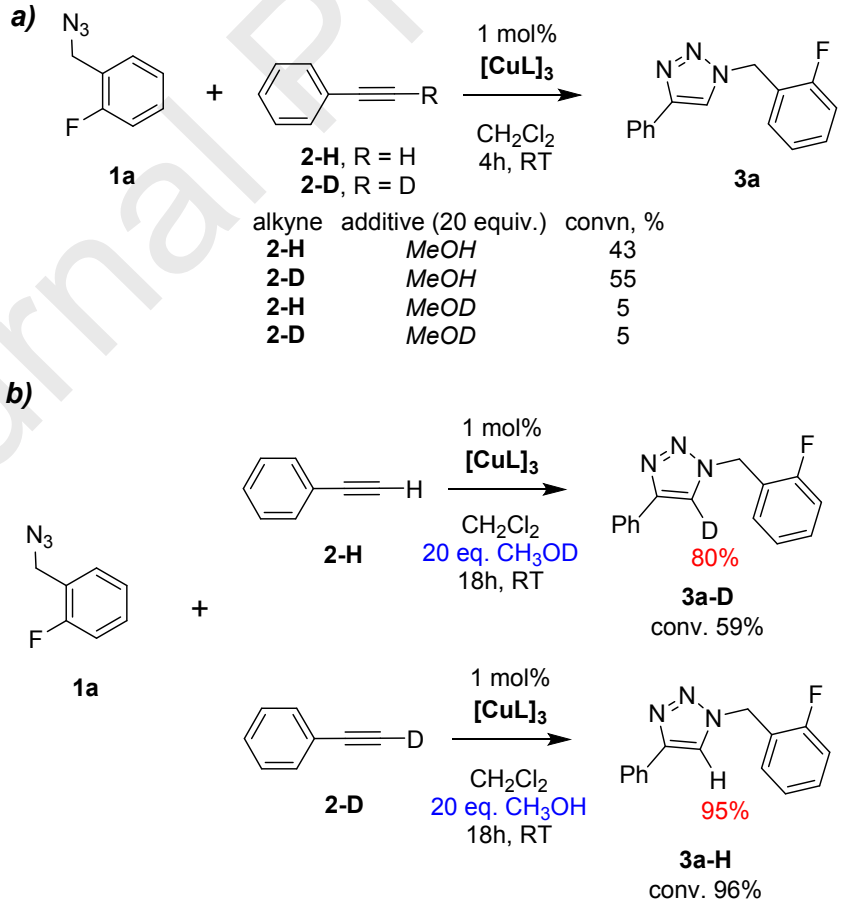


Figure 2. Plot of logV versus log[**[CuL]$_3$**] for CuAAC of *ortho*-fluorobenzyl azide **1a** and phenylacetylene **2** in CH_2Cl_2. Reaction conditions: azide **1a** (0.352 mmol), phenylacetylene **2** (0.352 mmol), catalyst **[CuL]$_3$** (0.5, 1, 2 and 4 mol%), CH_2Cl_2 (1.0 mL).

The kinetic significance of alkyne deprotonation revealed was further investigated to ascertain the rate-determining step (RDS) of the reaction using deuterium KIE experiments. A

primary deuterium KIE (k_H/k_D) of 1.1 was observed in the reaction in CH_2Cl_2 (see Fig. S9 in SI). This result is opposite to the commonly assumed mechanism,[13d,20b,20d] where the acetylide formation is RDS and, on another hand, supports the recent observation by Seath et al.,[21] where the RDS shifted to azide ligation/migratory insertion step. Next, we performed additional experiments using MeOH and MeOD as additives and involving phenylacetylenes **2-H** and **2-D** (deuterated). The reactions conducted in the presence of 20 equiv. MeOD gave the desired product **3a** only with a 5% conversion after 4 hours (Scheme 2a). In contrast, MeOH added lead to the formation of **3a** at 43% and 55% conversions, correspondingly (Scheme 2a). The reaction of phenylacetylene **2-H** with MeOD added gave the desired triazole **3a-D** in a 59% yield where 80% of deuterium was incorporated. A similar experiment with alkyne **2-D** in MeOH furnished the protonated triazole **3a-H** (95% proton incorporation) in a 96% yield (Scheme 2b). So, both experiments proved that the deprotonation of acetylene are occurred by forming the acetylide complex and, finally, the protonation of the triazole metallocycle by either with acetylene **2** or methanol has released the catalyst back to the catalytic cycle. Moreover, the presented experiments clearly show that the presence of protonating agents (MeOH or MeOD) in the reaction mixture makes difficult the deprotonation step by **[CuL]$_3$** shifting the equilibrium of deprotonated acetylene to it protonated form (see Scheme 2).



Scheme 2. Mechanistic investigations using phenylacetylenes **2-H** and **2-D**.

2.2 DFT calculations

To dissect the reaction mechanism, we have modeled the most likely routes of CuAAC reaction. The second order in the catalyst **[CuL]$_3$** suggests the participation of two copper(I) centers in the metallacycle formation step. For this purpose, we conducted a computational study to find the structure of the active catalytic particle.

Based on DFT calculations, we have found that the catalytically active particle is "bis-butterfly" tetranuclear complex $Cu_4L_4(RC{\equiv}CH)_2$ (**bb-S**, Fig. 3) which is formed from two molecules of its resting state – a binuclear "butterfly" **B**.[24] The complex **B** was previously isolated and characterized by a single crystal X-Ray analysis by Parasar et al.[6] Free energy of tetramer complex **bb-S** is lower than that of dimer **B** by 6.2 kcal/mol at experimental conditions. Complex **B** itself was also considered a catalytic particle but then the reaction has a very high energy barrier: 37.1 kcal/mol vs. 21.3 kcal/mol in case of **bb-S** (see Fig. 3 and S12 in SI). Complex **bb-S** as well as its "tetrahedral" counterpart (**th-S**) were isolated in previous studies.[6,10b] While **th-S** is 1.8 kcal/mol lower than **bb-S**, it also has much more sterically crowded copper atoms, so only **bb-S** appears to be able to attach an azide molecule. Thus, the catalytically active particle is **bb-S,** which exists in equilibrium with the catalytically inert **B** and **th-S**.

In our previous study, we have shown that also a 'spiro' complex **A** (in Figure 1) is catalytically active in this reaction.[5] This suggests that the complex can reorganize in the reaction mixture into the catalytic particle **B**, accompanied by Cu(II)Pz_2 precipitation. In this regard, it was observed by ESI-MS that the copper pyrazolate **[CuL]$_3$** can easily dissociate on different particles in solution (see Figures S1-S3 in SI).

Azide molecule attachment initiates Cu-Pz bond cleavage, during which leaving Pz ligand acts as a proton acceptor (Brønsted base), leading to the formation of the **IM2** complex. Proton transfer accompanying the azide-induced Cu-Pz bond cleavage has remarkably low activation energy (16.5 kcal/mol relative to **bb-S**), which explains the absence of H/D KIE in this reaction. This also explains the observed reaction inhibition by methanol (see Scheme 2), which likely protonates the pyrazole ligand after the bond cleavage preventing acetylene deprotonation.

Next, structure **IM2** undergoes cycloaddition to form a six-membered cycle (**IM3**). This transition state has relative energy of 21.3 kcal/mol, which makes it the rate limiting step of the studied reaction, as was proposed and proved by Seath et al.[21] At the next stage the second C-N bond forms via a 13.0 kcal/mol transition state, resulting in a five-membered triazole cycle (**IM4**). After that, the proton initially transferred to the Pz ligand returns to the carbon (**IM5**), product **P** exchanges for a new acetylene molecule and the catalytic particle is ready for the next cycle. The whole catalytic cycle and computed free energies along it are depicted in Fig. 3 (atomic coordinates and total energies are available in SI).

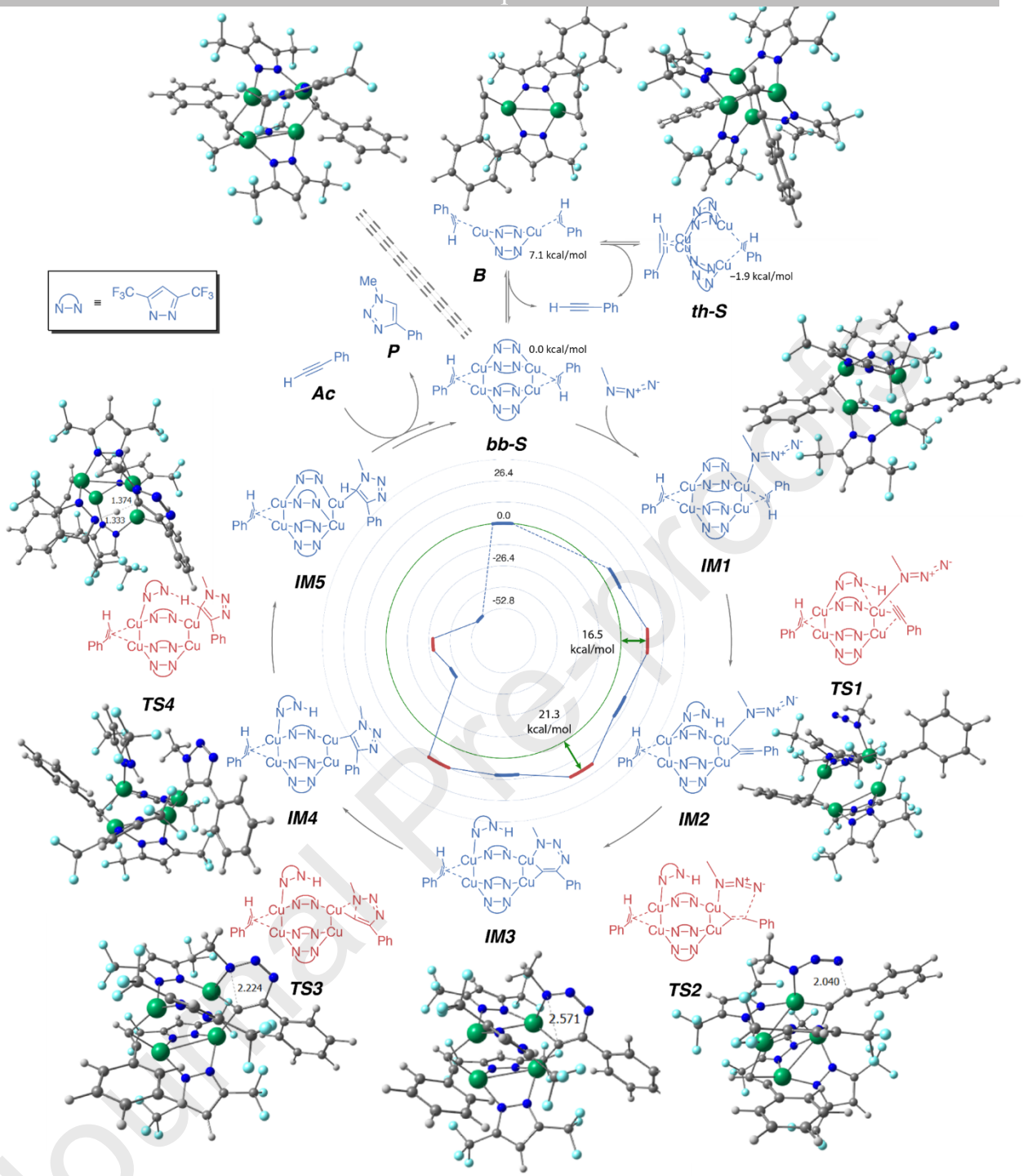


Figure 3. The catalytic cycle, its energetic diagram and some structures of stationary points along the reaction path. Energies of ***TS1*** and ***TS2*** relative to ***bb-S*** are shown on the diagram. All energy values are in kcal/mol, bond lengths are in Å.

Thus, the main mechanistic feature revealed by calculations is that the main catalytic particle is a "bis-butterfly" tetranuclear copper complex. Notably, while three pyrazolate molecules play roles of bidentate ligands that hold copper atoms side by side, the fourth pyrazolate molecule acts simultaneously as a monodentate ligand and as a Brønsted base deprotonating acetylene molecule. The computational results fully support the experimental data and confirm the

shift of the RDS from acetylide formation to azide ligation/migratory insertion. It was also proved that the reaction has a second-order dependence on the catalyst concentration where the two copper(I) centers participate in the metallacycle formation step from the "bis-butterfly" tetranuclear complex $Cu_4L_4(RC{\equiv}CH)_2$ formed from a complex **$[CuL]_3$** in the rate-determining step.[24]

2.3 Substrate scope

Next, with optimized conditions in hand, we have evaluated the scope and generality of the reaction with regard to variations of the azides and alkynes (Fig. 4). In all cases, the reaction practically doesn't depend on the electron effect of substituents furnishing 1,4-substituted triazoles **3a-j** (Fig. 4). The conversions are shown for all products because there is no formation of side products observed in the reaction.

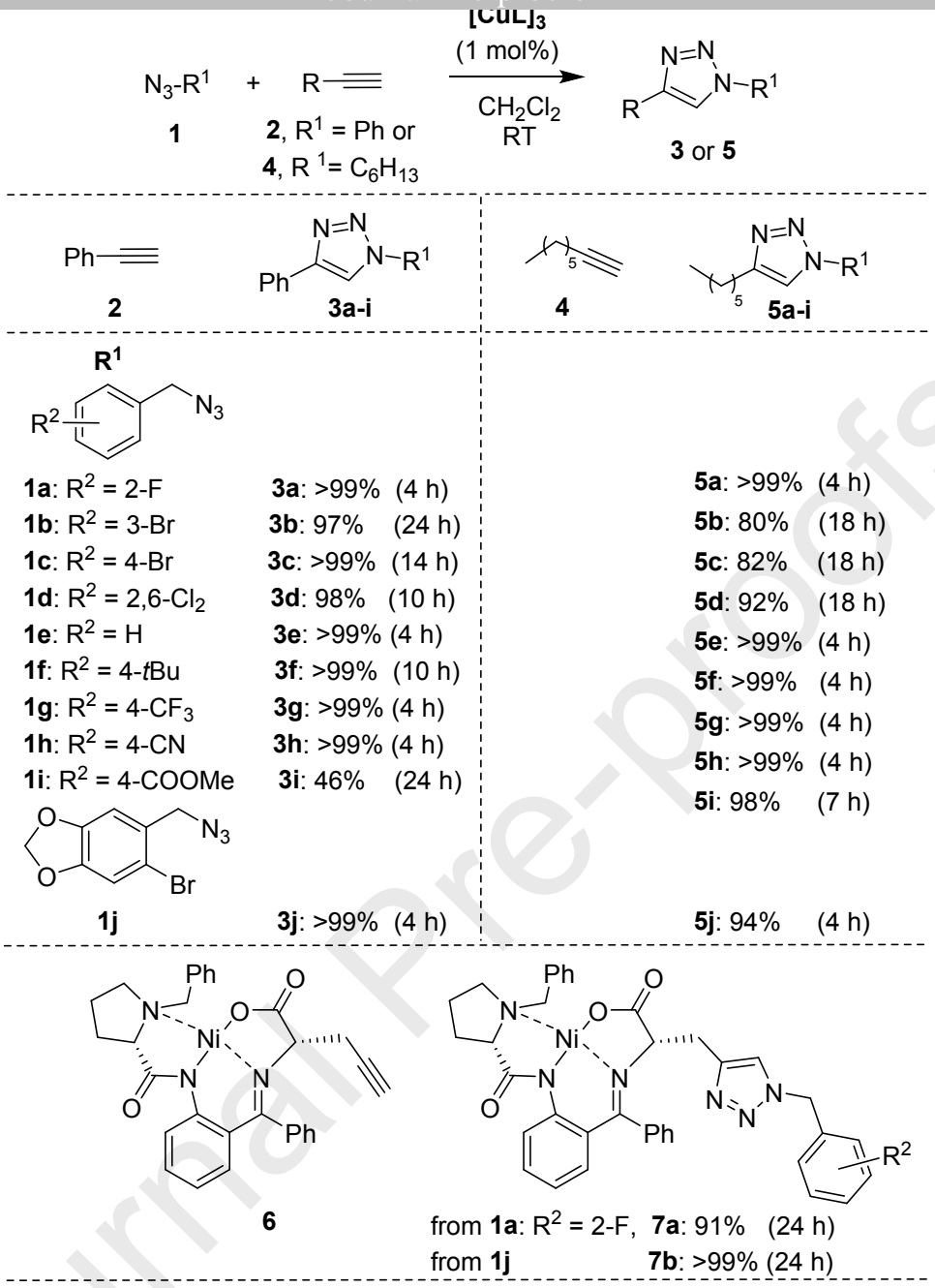


Figure 4. Substrate scope (for all products the conversions are given).

The click reactions of octyne-1 **4** with the same set of azides **1a-j** (Figure 4) were also successfully carried out. For most of the azides **5a-j**, apart from a few exceptions (products **5b-d**), comparable results were observed in terms of yields (80–>99%) as for phenylacetylene **2**.

Finally, to further emphasize the applicability and to demonstrate the practicability of the developed catalyst, we performed the reactions with a chiral Ni(II) complex **6** bearing an acetylene fragment in the side chain and azides **1a**,**j**. As we recently demonstrated,[25] the side chain modification of a chiral Ni(II) complex **6** *via* "click chemistry" leads to the amino acids with 1,2,3-triazole appendage that are interesting biologically active candidates.[15f,15h] However, the harsh conditions (DMSO, Et_3N and 70 °C) in our previous work, in some cases, furnished the desired

products in low yields.[25] Herein, the cycloaddition of the Ni(II) complex **6** with azides **1a** or **1j** in the presence of only 1 mol% catalyst **[CuL]$_3$** under mild conditions (RT, CH_2Cl_2) gave the desired products **7a** and **7b** in a 91% and >99% conversions *vs* previous our results (71% and 76% yields, correspondingly).[25] The obtained chiral Ni(II) complexes **7a** and **7b** after acidic decomposition give the corresponding valuable enantiopure 1,2,3-triazole containing (α)-amino acids.[25]

3. Conclusions

In summary, we have demonstrated that the trinuclear copper(I) pyrazolate complex **[CuL]$_3$** efficiently catalyzed an azide-alkyne cycloaddition reaction under relatively mild conditions. By experimental data and DFT calculations, we proved that the pyrazolate ligand in the copper complex acts as a Brønsted base and deprotonates the acetylene molecule for the successful reaction. The rate-determining step of the reaction is the first C-N bond formation between azide and acetylene (azide migratory insertion), as supported by DFT calculations. The reaction has second-order on copper suggesting that the two copper(I) centers participate in the metallacycle formation step. The connotation of the results is that the rate-determining step of CuAAC reactions can shift depending on the catalytic system and substrate class. This phenomenon was underestimated enough previously. Our finding nicely complements the recent observation by Seath et al.[21] where an alkyne-specific shift in a rate-determining step was evidenced depending on the structure of substrates. Furthermore, the developed method was applied for the synthesis of the scope of valuable 1,4-substituted 1,2,3-triazoles and amino acid derivatives bearing the triazole motif in high yields. The copper complex is robust, simple to prepare, and catalyzes the reaction even in water or without solvent (neat conditions). This work paves the way for the study of the CuAAC reaction mechanism and the design of new catalytic systems based on copper complexes.

4. Experimental section

4.1. General information

All solvents purchased from commercial suppliers were used without further purification (CH_2Cl_2, CD_2Cl_2, hexane, 1,2-dichloroethane, MeCN, MeOH). Solvents were distilled under an atmosphere of argon from sodium (THF, toluene). Purchased phenylacetylene (**2**) and 1-octyne (**4**) from commercial suppliers were used without further purification. The trinuclear copper(I) *bis*-(trifluoromethyl)pyrazolate (**[CuL]$_3$**) was prepared according to a published procedure.[26] Azides (**1**) was synthesized according to a literature procedure.[27] A chiral Ni(II) complex **6** was

available from our previous work.[25] If not stated otherwise, flash column chromatography was performed with silica gel 60 M from Macherey-Nagel.

4.2 Instrumentation

Proton nuclear magnetic resonance (^{1}H-NMR) spectra and carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz (^{1}H) and 101 MHz (^{13}C{^{1}H}). Chemical shifts are reported in ppm relative to the residual solvent peak ($CDCl_3$: δ = 7.26 ppm for ^{1}H-NMR, δ = 77.2 for ^{13}C-NMR). NMR data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant, integration, and nucleus. IR spectra were recorded on FT-IR Spectrometer Nicolet 6700 using CaF_2 cuvettes.

High-resolution mass spectra were registered on Bruker maXis QTOF instrument equipped with electrospray ionization (ESI) ion source. The measurements were performed in positive (HV capillary at 4.5 kV, spray shield offset at -0.5 kV) and negative (HV capillary at -4.0 kV, spray shield offset at -0.5 kV) modes with a scan range of m/z 50−2000. External calibration was performed using a low concentration tuning mix solution (Agilent Technologies). Direct syringe injection was used for all analyzed solutions in MeCN at a flow rate of 5 µL/min. Nitrogen was used as both nebulizer gas at 1 bar and dry gas at 4.0 L/min, 200 °C. All recorded spectra were processed using Bruker Data Analysis 4.0 software package.

4.3 DFT calculations

All calculations were performed at PBE0[28]-D3BJ[29]/def2-SVP[30]/PCM[31](CH_2Cl_2) level of theory in Gaussian16 program package.[32] PBE0 functional was selected as widely reliable and physically grounded.[33] The solvent effects of CH_2Cl_2 were implicitly accounted with the polarizable continuum model. Free energies were calculated with Head-Gordon[34] and Grimme[35] quasi-harmonic corrections implemented in GoodVibes 3.0.[36]

*4.4 General procedure for the click reaction between azides **1** and phenylacetylene **2** or 1-octyne (**4**) catalyzed by complex **[CuL]$_3$***

To a solution of complex **[CuL]$_3$** (1 mol%, 2.8 mg, 3.55 10^{-3} mmol) and acetylene **2** or **4** (0.352 mmol) in CH_2Cl_2 (1 mL) in a vial was added azide (**1**) (0.352 mmol) under air. The vial was then tightly capped with a rubber-sealed screw cap and the mixture was stirred at room temperature for 24 h. Afterward, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2) to afford the triazoles **3** or **5** as white powders.

The formation of products was confirmed by comparing the ^{1}H NMR data with literature reports (see in SI).

*4.5 General procedure for the click reaction between azides **1** and Ni(II) complex **6** catalyzed by complex **[CuL]$_3$***

To a solution of complex **[CuL]$_3$** (0.79 mg, 1 mol%, 1.0 10^{-3} mmol) and **6** (75 mg, 0.1 mmol) in CH_2Cl_2 (0.3 mL) in a vial was added azide **1a** or **1j** (0.12 mmol) under air. The vial was then tightly capped with a rubber-sealed screw cap and the mixture was stirred at room temperature for 24 h. Afterward, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/acetone (5:1)) to afford the Ni(II) complex with triazole appendage **9a** or **9b** as a red powder. The formation of products was confirmed by comparing the ^{1}H NMR data with literature reports (see in SI).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

V.A.L. directed the research. V.A.L and A.A.T. designed the experiments. A.R.S. carried out the majority of the synthetic experiments. V.A.L and A.A.T. performed kinetic experiments. A.A.L and M.G.M. performed the DFT calculations. A.M.T. performed the HRMS measurements. V.A.L, A.A.T., A.A.L., M.G.M., A.F.S., E.S.S. and V.I.M. performed data processing and analysis. V.A.L., A.A.T. and A.A.L. wrote the manuscript with feedback given by all contributors.

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Simulation and Data Processing for Mega-science Facilities at NRC "Kurchatov Institute", http://ckp.nrcki.ru/. The research is carried out using the equipment of the shared research facilities of HPC computing resources at Lomonosov Moscow State University.[37]

References

[1] For a review, see: (a) A.A. Titov, O.A. Filippov, L.M. Epstein, N.V. Belkova, E.S. Shubina, Inorg. Chim. Acta 470 (2018) 22–35; (b) J. Zheng, H. Yang, M. Xie, D. Li, Chem. Commun. 55 (2019) 7134–7146.

[2] (a) M.A. Omary, M.A. Rawashdeh-Omary, M.W.A. Gonser, O. Elbjeirami, T. Grimes, T.R. Cundari, H.V.K. Diyabalanage, C.S.P. Gamage, H.V.R. Dias, Inorg. Chem. 44 (2005) 8200–8210; (b) H.V.R. Dias, S. Singh, C.F. Campana, Inorg. Chem. 47 (2008) 3943–3945; (c) A.A. Titov, E.A. Guseva, A.F. Smol'yakov, F.M. Dolgushin, O.A. Filippov, I.E. Golub, A.I. Krylova, G.M. Babakhina, L.M. Epstein, E.S. Shubina, Russ. Chem. Bull. 62 (2013) 1829–1834; (d) N.B. Jayaratna, C.V. Hettiarachchi, M. Yousufuddin, H.V. Rasika Dias, New J. Chem. 39 (2015) 5092–5095; (e) O.A. Filippov, A.A. Titov, E.A. Guseva, D.A. Loginov, A.F. Smol'yakov, F.M. Dolgushin, N.V. Belkova, L.M. Epstein, E.S. Shubina, Chem. Eur. J. 21 (2015) 13176–13180; (f) A.A. Titov, E.A. Guseva, O.A. Filippov, G.M. Babakhina, I.A. Godovikov, N.V. Belkova, L.M. Epstein, E.S. Shubina, J. Phys. Chem. A 120 (2016) 7030–7036; (g) A.A. Titov, A.F. Smol'yakov, O.A. Filippov, I.A. Godovikov, D.A. Muratov, F.M. Dolgushin, L.M. Epstein, E.S. Shubina, Cryst. Growth Des. 17 (2017) 6770–6779.

[3] (a) S.-Z. Zhan, W. Chen, W. Lu, J. Zheng, F. Ding, T. Feng, D. Li, Inorg. Chem. 58 (2019) 1081–1090; (b) A.A. Titov, O.A. Filippov, A.F. Smol'yakov, K.F. Baranova, E.M. Titova, A.A. Averin, E.S. Shubina, Eur. J. Inorg. Chem. (2019) 821–827; (c) H.V. Rasika Dias, H.V.K. Diyabalanage, M.M. Ghimire, J.M. Hudson, D. Parasar, C.S. Palehepitiya Gamage, S. Li, M.A. Omary, Dalton Trans. 48 (2019) 14979–14983; (d) A.A. Titov, O.A. Filippov, A.F. Smol'yakov, I.A. Godovikov, JR. Shakirova, S.P. Tunik, I.S. Podkorytov, E.S. Shubina, Inorg. Chem. 58 (2019) 13, 8645–8656; (e) L.-R. Xing, Z. Lu, M. Li, J. Zheng, D. Li, J. Phys. Chem. Lett. 11 (2020) 2067–2073.

[4] (a) C. Di Nicola, F. Garau, Y.Y. Karabach, L.M.D.R.S. Martins, M. Monari, L. Pandolfo, C. Pettinari, A.J.L. Pombeiro, Eur. J. Inorg. Chem. (2009) 666–676; (b) B. Tu, Q. Pang, H. Xu, X. Li, Y. Wang, Z. Ma, L. Weng, Q. Li, J. Am. Chem. Soc. 139 (2017) 7998−8007.

[5] A.A. Titov, V.A. Larionov, A.F. Smol'yakov, M.I. Godovikova, E.M. Titova, V.I. Maleev, E.S. Shubina, Chem. Comm. 55 (2019) 290–293.

[6] D. Parasar, T.T. Ponduru, A. Noonikara-Poyil, N.B. Jayaratna, H.V. Rasika Dias, Dalton Trans. 48 (2019) 15782–15794.

[7] (a) A. Maspero, S. Brenna, S. Galli, A. Penoni, J. Organomet. Chem. 672 (2003) 123–129; (b) L. Wang, B. Guo, H.-X. Li, Q. Li, H.-Y. Li, J.-P. Lang, Dalton Trans. 42 (2013) 15570–15580.

[8] A.G. Mahmoud, L.M.D.R.S. Martins, M.F.C. Guedes da Silva, A.J.L. Pombeiro, Inorg. Chim. Acta 483 (2018) 371–378.

[9] C. Xu, T.H. Baum, Z. Wang, US Pat, US6417369B1, 2002.

[10] (a) N.B. Jayaratna, M.G. Cowan, D. Parasar, H.H. Funke, J. Reibenspies, P.K. Mykhailiuk, O. Artamonov, R.D. Noble, H.V. Rasika Dias, Angew. Chem. Int. Ed. 130 (2018) 16680–16684; (b) D. Parasar, R.M. Almotawa, N.B. Jayaratna, Y.S. Ceylan, T.R. Cundari, M.A. Omary, H.V. Rasika Dias, Organometallics 37 (2018) 4105–4118.

[11] (a) M. Meldal, C.W. Tornøe, Chem. Rev. 108 (2008) 2952–3015; (b) R. Buschbeck, P.J. Low, H. Lang, Coord. Chem. Rev. 255 (2011) 241–272; (c) X. Wang, X. Wang, X. Wang, J. Zhang, C. Liu, Y. Hu, Chem. Rec. 17 (2017) 1231–1248.

[12] For reviews on CuAAC, see: (a) P. Wu, V.V. Fokin, Aldrichimica Acta 40 (2007) 7–17; (b) J.E. Hein, V.V. Fokin, Chem. Soc. Rev. 39 (2010) 1302–1315; (c) F. Wei, W. Wang, Y. Ma, C.-H. Tung, Z. Xu, Chem. Commun. 52 (2016) 14188–14199; (d) Z. Chen, Z. Liu, G. Cao, H. Li, H. Ren, Adv. Synth. Catal. 359 (2017) 202–224.

[13] For selected examples on CuAAC, see: (a) V.V. Rostovtsev, L.G. Green, V.V. Fokin, K. B. Sharpless, Angew. Chem. Int. Ed. 41 (2002) 2596–2599; (b) C.W. Tornoe, C. Christensen, M. Meldal, J. Org. Chem. 67 (2002) 3057–3064; (c) F. Himo, T. Lovell, R. Hilgraf, V.V. Rostovtsev, L. Noodleman, K.B. Sharpless, V.V. Fokin, J. Am. Chem. Soc. 127 (2005) 210–216; (d) V.O. Rodionov, V.V. Fokin, M. G. Finn, Angew. Chem. Int. Ed. 44 (2005) 2210–2215; (e) L. Li, G. Zhang, A. Zhu, L. Zhang, J. Org. Chem. 73 (2008) 3630–3633; (f) J.E. Hein, J.C. Tripp, L. Krasnova, K.B. Sharpless, V.V. Fokin, Angew. Chem. Int. Ed. 48 (2009) 8018–8021; (g) G.C. Kuang, P.M. Guha, W.S. Brotherton, J.T. Simmons, L.A. Stankee, B.T. Nguyen, R.J. Clark, L. Zhu, J. Am. Chem. Soc. 133 (2011) 13984–14001; (h) J. Jin, E.A. Romero, M. Melaimi, G. Bertrand, J. Am. Chem. Soc. 137 (2015) 15696–15698.

[14] For a review, see: P. Thirumurugan, D. Matosiuk, K. Jozwiak, Chem. Rev. 113 (2013) 4905–4979.

[15] For therapeutic activity of triazole-containing compounds, see: (a) D.R. Buckle, C.J.M. Rockell, H. Smith, B.A. Spicer, J. Med. Chem. 29 (1986) 2262–2267; (b) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.F. Perno, A. Karlsson, J. Balzarini, M.J. Camarasa, J. Med. Chem. 37 (1994) 4185–4194; (c) M.D. Chen, S.J. Lu, G.P. Yuan, S.Y. Yang, X.L. Du, Heterocycl. Commun. 6 (2000) 421–426; (d) M.J. Genin, D.A. Allwine, D.J. Anderson, M.R. Barbachyn, D.E. Emmert, S.A. Garmon, D.R. Graber, K.C. Grega, J.B. Hester, D.K. Hutchinson, J. Morris, R.J. Reischer, C.W. Ford, G.E. Zurenko, J.C. Hamel, R.D. Schaadt, D.

Stapert, B.H. Yagi, J. Med. Chem. 43 (2000) 953–970; (e) H.C. Kolb, B.K. Sharpless, Drug Discov. Today 8 (2003) 1128–1137; (f) N.J. Stanley, D.S. Pedersen, B. Nielsen, T. Kvist, J.M. Mathiesen, H. Bräuner-Osborne, D.K. Taylor, A.D. Abell, Bioorg. Med. Chem. Lett. 20 (2010) 7512–7515; (g) J. Doiron, A.H. Soultan, R. Richard, M.M. Touré, N. Picot, R. Richard, M. Cuperlovic-Culf, G.A. Robichaud, M. Touaibia, Eur. J. Med. Chem. 46 (2011) 4010–4024; (h) T. Boibessot, D. Bénimèlis, M. Jean, Z. Benfodda, P. Meffre, Synlett 27 (2016) 2685–2688; (i) A.H. Tarawneh, L.A. Al-Momani, F. León, S.K. Jain, A.V. Gadetskaya, S.T. Abu-Orabi, B.L. Tekwani, S.J. Cutler, Med. Chem. Res. 27 (2018) 1269–1275; (j) F.J. Smit, R. Seldon, J. Aucamp, A. Jordaan, D.F. Warner, D.D. N'Da, Med. Chem. Res. 28 (2019) 2279–2293.

[16] R.A. Decréau, J.P. Collman, A. Hosseini, Chem. Soc. Rev. 39 (2010) 1291–1301.

[17] J.-F. Lutz, Angew. Chem. Int. Ed. 46 (2007) 1018–1025.

[18] P.-Z. Li, X.-J. Wang, Y. Zhao, Coord. Chem. Rev. 380 (2019) 484–518.

[19] For reviews, see: (a) R. Berg, B.F. Straub, Beilstein J. Org. Chem. 9 (2013) 2715–2750; (b) C. Wang, D. Ikhlef, S. Kahlal, J.-Y. Saillard, D. Astruc, Coord. Chem. Rev. 316 (2016) 1−20.

[20] (a) V.O. Rodionov, S.I. Presolski, D. Díaz Díaz, V.V. Fokin, M.G. Finn, J. Am. Chem. Soc. 129 (2007) 12705-12712; (b) B.T. Worrell, J.A. Malik, V.V. Fokin, Science 340 (2013) 457–460; (c) Y. Özkılıç, N.Ş. Tüzün, Organometallics 35 (2016) 2589−2599; (d) X. Zhang, P. Liu, L. Zhu, Molecules 21 (2016) 1697; (e) M.S. Ziegler, K.V. Lakshmi, T.D. Tilley, J. Am. Chem. Soc. 139 (2017) 5378–5386; (f) C. Özen, N.Ş. Tüzün, J. Mol. Cat. A: Chemical 426 (2017) 150-157; (g) S.N. Semenov, L. Belding, B.J. Cafferty, M.P.S. Mousavi, A.M. Finogenova, R.S. Cruz, E.V. Skorb, G.M. Whitesides, J. Am. Chem. Soc. 140 (2018) 10221–10232; (h) R. Chung, A. Vo, V.V. Fokin, J.E. Hein, ACS Catal. 8 (2018) 7889−7897; (i) H.B.E. Ayouchia, L. Bahsis, H. Anane, L.R. Domingo, S.-E. Stiriba, RSC Adv. 8 (2018) 7670−7678; (j) H. Chen, C. Soubra-Ghaoui, Z. Zhu, S. Li, T.A. Albright, C. Cai, J. Catal. 361 (2018) 407−413; (k) P.J. Silva, C.E.P. Bernardo, J. Phys. Chem. A 122 (2018) 7497−7507; (l) Y.-C. Lin, Y.-J. Chen, T.-Y. Shih, Y.-H. Chen, Y.-C. Lai, M.Y. Chiang, G.C. Senadi, H.-Y. Chen, H.-Y. Chen, Organometallics 38 (2019) 223−230; m) R. Roohzadeh, B. Nasiri, A. Chipman, B.F. Yates, A. Ariafard, Organometallics 38 (2019) 256−267.

[21] C.P. Seath, G.A. Burley, A.J.B. Watson, Angew. Chem. Int. Ed. 56 (2017) 3314−3318.

[22] (a) C. Glaser, Ber. Dtsch. Chem. Ges. 2 (1869) 422–424; (b) C. Glaser, Ann. Chem. Pharm. 154 (1870) 137–171; (c) P. Siemsen, R.C. Livingston, F. Diederich, Angew. Chem. Int. Ed. 39 (2000) 2632–2657.

[23] (a) B.F. Straub, Chem. Commun. (2007) 3868–3870; (b) M. Ahlquist, V.V. Fokin, Organometallics 26 (2007) 4389–4391.

[24] V.A. Larionov, L.V. Yashkina, M.G. Medvedev, A.F. Smol'yakov, A.S. Peregudov, A.A. Pavlov, D.B. Eremin, T.F. Savel'yeva, V.I. Maleev, Y.N. Belokon, Inorg. Chem. 58 (2019) 11051–11065.

[25] V.A. Larionov, H.V. Adonts, Z.T. Gugkaeva, A.F. Smol'yakov, A.S. Saghyan, M.S. Miftakhov, S.A. Kuznetsova, V.I. Maleev, Y.N. Belokon, ChemistrySelect 3 (2018) 3107–3110.

[26] H. V. Rasika Dias, S. A. Polach, Z. Wang, J. Fluor. Chem. 103 (2000) 163–169.

[27] C. Büll, T. Heise, N. van Hilten, J.F.A. Pijnenborg, V. Bloemendal, L. Gerrits, E.D. Kers-Rebel, T. Ritschel, M.H. den Brok, G.J. Adema, T.J. Boltje, Angew. Chem. In. Ed. 56 (2017) 3309–3313.

[28] C. Adamo, V. Barone, J. Chem. Phys. 110 (1999) 6158–6170.

[29] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, J. Chem. Phys. 132 (2010) 154104.

[30] F. Weigend, R. Ahlrichs, Phys. Chem. Chem. Phys. 7 (2005) 3297–3305.

[31] B. Mennucci, Wiley Interdiscip. Rev. Comput. Mol. Sci. 2 (2012) 386–404.

[32] Gaussian 16, Revision C.01, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, G.A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A.V. Marenich, J. Bloino, B.G. Janesko, R. Gomperts, B. Mennucci, H.P. Hratchian, J.V. Ortiz, A.F. Izmaylov, J.L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V.G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J.A. Montgomery, Jr., J.E. Peralta, F. Ogliaro, M.J. Bearpark, J.J. Heyd, E.N. Brothers, K.N. Kudin, V.N. Staroverov, T.A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A.P. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, J.M. Millam, M. Klene, C. Adamo, R. Cammi, J.W. Ochterski, R.L. Martin, K. Morokuma, O. Farkas, J.B. Foresman, D.J. Fox, Gaussian, Inc., Wallingford CT, 2016.

[33] (a) M.G. Medvedev, I.S. Bushmarinov, J. Sun, J.P. Perdew, K.A. Lyssenko, Science 355 (2017) 49; (b) N. Mardirossian, M. Head-Gordon, Mol. Phys. 115 (2017) 2315–2372; (c) A.A. Marjewski, M.G. Medvedev, I.S. Gerasimov, M.V. Panova, J.P. Perdew, K.A. Lyssenko, A.O. Dmitrienko, Mendeleev Commun. 28 (2018) 225–235.

[34] Y.-P. Li, J. Gomes, S. Mallikarjun Sharada, A. T. Bell, M. Head-Gordon, J. Phys. Chem. C 119 (2015) 1840–1850.

[35] S. Grimme, Chem. Eur. J. 18 (2012) 9955–9964.

[36] G. Luchini, J.V. Alegre-Requena, I. Funes-Ardoiz, R.S. Paton, F1000Research 9 (2020) 291.

[37] V. Sadovnichy, A. Tikhonravov, V. Voevodin, V. Opanasenko, Chapman & Hall/CRC Computational Science; CRC Press: Boca Raton, USA, 2013, 283–307.

- Trinuclear copper(I) pyrazolate efficiently catalyses CuAAC under mild conditions
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- Rate-determining step of the reaction is the azide migratory insertion
- RDS of CuAAC reactions can depend on catalytic system and substrate class
- Catalytic system is applicable for the synthesis of amino acids bearing triazole motif