Water-Compatible Synthesis of 1,2,3-Triazoles under Ultrasonic Conditions by a Cu(I) Complex-Mediated Click Reaction

Juan-Carlos Castillo, Nestor-Fabian Bravo, Lenka-Victoria Tamayo, Paula-Daniela Mestizo, John Hurtado,* Mario Macías, and Jaime Portilla*

Cite This: ACS Omega 2020, 5, 30148−30159

ABSTRACT: A new monophosphine Cu(I) complex bearing bis(pyrazolyl)methane (L₁) (CuL₁PPh₃) was synthesized and used as a catalyst for the three-component click reaction from an alkyl halide, sodium azide, and terminal alkyne to furnish 1,4-disubstituted 1,2,3-triazoles in up to 93% yield. The catalyst is highly stable, compatible with oxygen/water, and works with total efficiency under ultrasonic condition. The structure of the complex was studied and confirmed by X-ray crystallography, finding a riveting relationship with its catalytic activity. This sustainable triazoles synthesis is distinguished by its high atom economy, low catalyst loading (up to 0.5 mol %), broad substrate scope, short reaction times, operational simplicity, and an easy gram-scale supply of a functionalized product for subsequent synthetic applications.

INTRODUCTION

Sustainable laboratory methods have become the main route for synthetic chemists to carry out research, which had led scientists to improve the scope of their discoveries and reduce pollution during chemical production.¹−⁵ Efficient reactions, catalyst use, and water-compatible and/or alternative activation technologies are crucial to minimize cost, energy, environmental impact, and waste. Ultrasound or microwave irradiation (USI or MWI) and mechanochemical mixing are powerful tools in the current sustainable organic synthesis and have been successfully used to expand traditional methods, and thus a plethora of applications have been reported.²,³ Specifically, ultrasonic synthesis has emerged as one of the most appreciated techniques due to its advantages with respect to conventional thermal methods, such as reaction rate, yield, operational simplicity, purity of the products, and so on.³⁻⁵

Regarding efficient reactions and catalyst use, laboratories of Sharpless (in situ Cu(I) formation from CuSO₄/sodium ascorbate)⁶ and Meldal (Cu/DPPEA)⁷ independently reported that Cu(I) can catalyze the Huisgen cycloaddition to afford 1,4-disubstituted 1,2,3-triazoles under very mild conditions. This reaction satisfies all of the requirements of the term “click chemistry” and is known as copper-catalyzed azide−alkyne cycloaddition (CuAAC).⁸ This reaction has been effectively applied in diverse divisions of science such as organic chemistry,⁹⁻¹⁰ drug discovery,¹¹,¹² polymers,¹³ and material sciences¹⁴ because of its ideal atom economy, bio-orthogonality, regiospecificity, high yield, and compatibility with diverse functional groups. Moreover, they are important reports of the click reaction carried out in easily removable or benign solvents such as water.¹⁵

The catalytic system most commonly used for CuAAC employs in situ formation of Cu(I) by the reduction of Cu(II) salts with sodium ascorbate (NaAsc) in water.⁶ Afterward, direct ditization of Cu(I) salts in the presence of Cu(I)-stabilizing N-heterocyclic ligands such as 2,6-bis(2-oxazolinyl)pyridine I¹⁶ and tris(triazolyl)amine-bearing ligands II¹⁷,¹⁸ has been widely applied to protect Cu(I) from oxidation and disproportionation (Figure 1). Alternatively, the use of preformed Cu(I) complexes

Received: September 18, 2020
Accepted: October 16, 2020
Published: November 12, 2020
bearing tri(triazol-4-yl)methane-based ligands III has offered unprecedented practicability to catalyze the CuAAC reaction because the tertiary nitrogen (N) atom center of the catalyst behaves both as a donor to Cu(I) and as a proton acceptor. Thus, there is no requirement of a base and deoxygenated conditions (Figure 1).

In the last decade, phosphorus-based Cu(I) complexes including CuBr(PPh3)3,20 CuI[P(OEt)3] and Cu(NO3)(PPh3)2,21 and CuBr[PPh2(OPh-2-OMe)]22 have been used to prepare various 1,2,3-triazoles under very mild reaction conditions. Albeit the use of preformed complexes bearing N-donor ligands or phosphine derivatives has undeniably increased the CuAAC reaction impact, both synthesis and application efficiency of novel catalysts are still desirable.15−23 Indeed, we have recently reported the synthesis of a Cu(I) coordination polymer [Cu2(μ-I)2(μ-L)2]n by a self-assembly process between CuI and 1,3-bis(benzotriazol-1-ylmethyl)benzene, as well as its application in the three-component reaction between benzyl bromides, sodium azide (2), and terminal alkynes in acetonitrile to furnish 1,2,3-triazoles 4 (Scheme 1a).23 Despite the ubiquity of the CuAAC reaction, there are a few reports of three-component variants involving in situ generation of organic azides by alternative techniques such as ultrasound, microwave, and continuous flow conditions in aqueous media.24−26 For example, Sreedhar,25 Mady,26 and Rezki27 reported 1,2,3-triazoles synthesis in reduced reaction times (6−60 min) using ultrasonic baths but in the presence of additives and a high catalyst loading (Scheme 1b). Though there are reports on the application of ultrasonic baths as energy sources to promote chemical reactions, use of a probe-based ultrasonic system allowing excellent parameter control is valuable. Moreover, the probe favors an efficient sonication process because of its highly localized intensity, which means it would be easy to reproduce or scale a given process.28

Thus far, there has only been one published example of the multicomponent click reaction using ultrasonic homogenizer (Scheme 1b).28 Albeit such sonochemical methods are generally reliable in aqueous medium, most of them employ ultrasonic baths,25−27 organic co-solvents,26−28 one or more reagents in excess of the stoichiometric amount, and require much larger quantities of CuSO4, NaAsc, and CuI because the absence of Cu(I)-stabilizing ligands increases the metal center oxidation. To overcome these drawbacks, and due to our interest in sustainable laboratory methods to obtain diverse N-heterocyclic compounds,29−31 we report here the preparation of a novel Cu(I) complex bearing triphenylphosphine (PPh3) and bis(3,5-dimethyl-1H-pyrazol-1-yl)methane ligands and their application in the multicomponent click reaction in aqueous media employing an ultrasonic homogenizer (Scheme 1c).

**RESULTS AND DISCUSSION**

To achieve a detailed methodological study, we prepare a new Cu(I) complex bearing bis(3,5-dimethyl-1H-pyrazol-1-yl)methane (L1) and PPh3 ligands (CuL1PPh3). Initially, the
ligand L1 was synthesized under known conditions in 68% yield (i.e., 3,5-dimethylpyrazole, KOH, K2CO3, and Bu4NBr in DCM).32 The Cu(I) halide complexes having tertiary phosphine ligands with 1:1, 1:2, 1:3, and 2:3 Cu/PR3 ratios have been synthesized, and their structures are determined by X-ray crystallography (XRC).33 The stoichiometry ratio determines the nuclearity of the complexes, while the polymorph outcome can be influenced by the solvent or the procedure used.34 Complexes with a 1:1 Cu/Ligand [CuX(PR3)] ratio only have been obtained in a tetrameric structure form, as polymorphs are cubane-like or step-like.34 Following the previously reported method,35 we synthesized the complex [CuI(PPh3)]4 (A) in 76% yield employing a 1:1 molar ratio stoichiometry of CuI and PPh3 in acetonitrile (MeCN) at room temperature for 1 h (Scheme 2a). XRC analysis confirmed that this Cu(I) cluster was obtained as a step-like polymorph in a tetrameric structure form (Scheme 2a; see the Supporting Information (SI) for structural details).

The new complex CuIL1PPh3 (B) having the ligand L1 was synthesized in 54% yield after its recrystallization from MeCN at room temperature. Albeit mass spectrometry studies were carried out to establish the new complex stoichiometry, the result was inconclusive. Fortunately, we obtained single crystals suitable for XRC analysis of the complex that confirmed a 1:1 Cu/L1 ratio regardless of the stoichiometry of the reaction. These results are consistent with those found with Cu(I) complexes having neutral bidentate N-donor ligands.36 This complex is stable in air for extended periods of time in the solid state and for several days in solution (Scheme 2b; see the SI for structural details).

The 1H and 13C NMR spectra of CuIL1PPh3 were measured in DMSO-d6 and the appropriate signals of hydrogen and carbon atoms of the ligands L1 and PPh3 were observed (see Figures S5 and S6 in the SI). The clear downfield shifts of the methylene group and pyrazolyl ring protons may be explained by increased σ-bonding contribution from the N-donor L1 to the Cu(I) center. Moreover, the multiplet at 7.38–7.49 ppm integrating for 15 hydrogens confirmed that the complexes have a PPh3 group. The 13C NMR spectrum showed that carbons of the two pyrazolyl rings are equivalent, which support the tetrahedral geometry of complex. Notably, the shift to higher field of ipso-carbons (δ = 133.2 ppm) of the PPh3 in complex with respect to free PPh3 (δ = 136.6 ppm) could be explained by increased π-backbonding influence from the metal to PPh3 ligand, which is consistent with the shorter Cu–P bond length of 2.21 Å (Table S2 in the SI).37

The two synthesized Cu(I) complexes were subsequently studied with respect to their catalytic properties in the three-component click reaction to furnish 1,2,3-triazoles. First, we studied the synthesis of noncommercially available terminal alkynes employing a previously reported method in our laboratory.38 In this way, we established an efficient Cs2CO3-promoted method for the O-alkylation of hydroxyaromatic compounds 5a–d and the N-alkylation of benzylamine (5d) with propargyl bromide (6) in anhydrous N,N-dimethylformamide (DMF) at 25 °C for 12 h.39 2.0 equiv of 5d was used.

Scheme 2. Synthesis of Complexes (a) [CuI(PPh3)]4 and (b) CuIL1PPh3, and Their X-ray Structures

Scheme 3. Cs2CO3-Promoted Chemoselective Alkylation of 5a–d.a,b

The reaction conditions: equimolar amounts (6.77 mmol) of 5a–d, propargyl bromide 6, and Cs2CO3 in 5.0 mL of DMF at 25 °C for 12 h. b 2.0 equiv of 5d was used.

The 1H and 13C NMR spectra of CuIL1PPh3 were measured in DMSO-d6 and the appropriate signals of hydrogen and carbon atoms of the ligands L1 and PPh3 were observed (see Figures S5 and S6 in the SI). The clear downfield shifts of the methylene group and pyrazolyl ring protons may be explained by increased σ-bonding contribution from the N-donor L1 to the Cu(I) center. Moreover, the multiplet at 7.38–7.49 ppm integrating for 15 hydrogens confirmed that the complexes have a PPh3 group. The 13C NMR spectrum showed that carbons of the two pyrazolyl rings are equivalent, which support the tetrahedral geometry of complex. Notably, the shift to higher field of ipso-carbons (δ = 133.2 ppm) of the PPh3 in complex with respect to free PPh3 (δ = 136.6 ppm) could be explained by increased π-backbonding influence from the metal to PPh3 ligand, which is consistent with the shorter Cu–P bond length of 2.21 Å (Table S2 in the SI).37

The two synthesized Cu(I) complexes were subsequently studied with respect to their catalytic properties in the three-component click reaction to furnish 1,2,3-triazoles. First, we studied the synthesis of noncommercially available terminal alkynes employing a previously reported method in our laboratory.38 In this way, we established an efficient Cs2CO3-promoted method for the O-alkylation of hydroxyaromatic compounds 5a–c and the N-alkylation of benzylamine (5d) with propargyl bromide (6) in anhydrous N,N-dimethylformamide (DMF) at 25 °C for 12 h for obtaining functionalized terminal alkynes 3e–h in good yields (Scheme 3). In all examples, the purity was >95% by 1H NMR analysis of the crude reaction mixtures.

Scheme 3. Cs2CO3-Promoted Chemoselective Alkylation of 5a–d.a,b

The reaction conditions: equimolar amounts (6.77 mmol) of 5a–d, propargyl bromide 6, and Cs2CO3 in 5.0 mL of DMF at 25 °C for 12 h. b 2.0 equiv of 5d was used.
Afterward, benzyl bromide (1a), sodium azide (2), and phenylacetylene (3a) were chosen as model substrates aiming to explore the Cu(I) complexes obtained in the synthesis of 1-benzyl-4-phenyl-1H-1,2,3-triazole (4a). All experiments were performed using normal atmospheric conditions and stoichiometric amounts of the reagents (Table 1). First, we tested the reaction with a range of temperatures, solvents, Cu(I) catalysts, and by examining the effect of USI compared to conventional heating to define the best reaction conditions. Both [CuI(PPh₃)]₄ and CuIL₁PPh₃ complexes were tested in various experiments at the same time to find the best catalytic system. In all cases, the expected product 4a was observed exclusively, by ¹H NMR analysis of the crude reaction mixtures, without any nitrogen-based ligand/additive (Table 2). The reactions by USI were performed using an ultrasonic reactor (Vibra-Cell VCX 750 probe) in pulse mode at 20 kHz and 40% wave amplitude. When CuIL₁PPh₃ loading was decreased down to 1 mol %, excellent conversions were still obtained keeping the reaction time and ultrasonic power (Table 2, entries 1–4), and only a moderate conversion into 4a was obtained with 0.5 mol % catalyst (Table 2, entry 5). Moreover, decreasing the reaction time and US power while maintaining the catalyst loading led to moderate conversions (Table 2, entries 6–9). These results suggest that the best reaction conditions are achieved when it is sonicated in the presence of 1 mol % catalyst for 30 min in aqueous medium (Table 1, entry 11–12). From these optimized reaction conditions, we tested the ligand effect on [CuI(PPh₃)]₄ and CuIL₁PPh₃ complexes were tested in various experiments at the same time to find the best catalytic system. In all cases, the expected product 4a was observed exclusively, by ¹H NMR analysis of the crude reaction mixtures, without any nitrogen-based ligand/additive (Table 2). The reactions by USI were performed using an ultrasonic reactor (Vibra-Cell VCX 750 probe) in pulse mode at 20 kHz and 40% wave amplitude. When CuIL₁PPh₃ loading was decreased down to 1 mol %, excellent conversions were still obtained keeping the reaction time and ultrasonic power (Table 2, entries 1–4), and only a moderate conversion into 4a was obtained with 0.5 mol % catalyst (Table 2, entry 5). Moreover, decreasing the reaction time and US power while maintaining the catalyst loading led to moderate conversions (Table 2, entries 6–9). These results suggest that the best reaction conditions are achieved when it is sonicated in the presence of 1 mol % catalyst for 30 min in aqueous medium (Table 2, entry 4). From these optimized reaction conditions, we tested the ligand effects by using them in combination with the Cu(I) catalyst (Table 3). The addition of 10 mol % free ligands (PPh₃ and/or L₁) to the reaction mixtures having CuIL₁PPh₃ (1 mol %) had little effect in conversions

Table 1. Optimization of the Best Solvent, Catalyst, and Temperature for Triazole 4a Synthesis

| entry | solvent | catalyst | T (°C) | conv (%) |
|-------|---------|----------|--------|---------|
| 1     | H₂O     | CuI[PPh₃]₄ (A) | 40     | ND      |
| 2     | THF     | CuI[PPh₃]₄ (A) | 40     | 71 (66) |
| 3     | MeCN    | CuI[PPh₃]₄ (A) | 40     | 78 (73) |
| 4     | EtOH    | CuI[PPh₃]₄ (A) | 40     | 80 (74) |
| 5     | H₂O     | CuI[PPh₃]₄ (A) | 40     | 88 (81) |
| 6     | H₂O     | CuI[PPh₃]₄ (A) | 40     | 56 (51) |
| 7     | H₂O     | CuI[PPh₃]₄ (A) | 60     | >98 (92)|
| 8     | H₂O     | CuI[PPh₃]₄ (A) | 60     | >98 (>98)|
| 9     | H₂O     | CuI[PPh₃]₄ (A) | 60     | 40 (35) |
| 10    | H₂O     | CuI[PPh₃]₄ (A) | 90     | 92 (87) |
| 11    | H₂O     | CuI[PPh₃]₄ (A) | 60     | 97 (90) |
| 12    | H₂O     | CuI[PPh₃]₄ (A) | 30     | 70 (64) |
| 13    | H₂O     | CuCl      | 60     | 30      |
| 14    | H₂O     | CuBr      | 60     | 37      |
| 15    | H₂O     | CuI       | 60     | 51      |
| 16    | H₂O     | CuOAc     | 60     | 54      |
| 17    | H₂O     | CuSO₄/NaAsc | 60     | 42      |

All experiments were performed with equimolar amounts (0.50 mmol) of 1a, 2, and 3a, and 5 mol % catalyst in 2.0 mL of solvent under stirring for 6 h by conventional heating. Conversions were determined by ¹H NMR of the crude reaction mixtures using CH₃Br₂ as an internal standard, and those shown in parentheses were obtained with [CuI(PPh₃)]₄ (A). Triazole was undetectable by ¹H NMR of the crude reaction mixture. Reaction time 12 h. Reaction under US irradiation (20 kHz, 300 W) at 60 °C for 30 min.

In a modified protocol, we carried out the reaction under USI to furnish a slightly lower yield in a shorter reaction time than under conventional heating based on thermal conduction and convection (Table 1, entry 11 vs 7). The shorter reaction time could be due to ultrasonic cavitation by the probe immersed in the reaction mixture, which enhances mass transfer rates and catalyst efficacy. In this process, an inverse temperature effect on cavitation intensity takes place due to generation of vaporeous cavities, reduced bubble collapse, and thus high boiling solvents are ideal for reactions that require high temperatures. Consequently, the effect of temperature was evaluated keeping the same reaction time, but the conversion of 4a significantly diminished at lower temperatures (Table 1, entry 11 vs 12). In all cases, [CuI(PPh₃)]₄ showed a catalytic activity somewhat lower than that of CuIL₁PPh₃ (Table 1, entries 2–12), though the conversion largely decreased in the presence of Cu(I) salts without any additive, as well as with the most commonly used catalytic system CuSO₄/NaAsc (Table 1, entries 13–17). Pleasantly, the US-assisted reaction in water resulted in the total starting materials conversion into 4a in the presence of 5 mol % CuIL₁PPh₃ (Table 1, entry 11).

Aiming to improve the process, we screened the catalyst loading, reaction time, and ultrasound power in the absence of any nitrogen-based ligand/additive (Table 2). The reactions by

Table 2. Optimization of Catalytic Load and US Power for Triazole 4a Synthesis

| entry | power (W) | [Cu] (mol %) | t (min) | conv (%) |
|-------|-----------|--------------|---------|---------|
| 1     | 300       | 4            | 30      | >96     |
| 2     | 300       | 3            | 30      | >96     |
| 3     | 300       | 2            | 30      | >96     |
| 4     | 300       | 1            | 30      | 95      |
| 5     | 300       | 0.5          | 30      | 63      |
| 6     | 300       | 1            | 20      | 70      |
| 7     | 300       | 1            | 10      | 41      |
| 8     | 200       | 1            | 30      | 64      |
| 9     | 100       | 1            | 30      | 39      |

Experiments were performed with equimolar amounts (0.50 mmol) of 1a, 2, and 3a, and 0.5–4 mol % catalyst in 2.0 mL of distilled water under USI (20 kHz, 100–300 W) at 60 °C for 10–30 min. Conversions were determined by ¹H NMR using CH₂Br₂ as an internal standard.
Using 1 mol % Cu(I) catalyst, the new preformed complex CuIL1PPh3 achieved the best catalytic result with respect to its precursor [CuI(PPh3)]4 and the possible in situ generation of CuIL1PPh3 (Table 2, entry 4 vs Table 3, entries 4−6).39,40 We think this might be due to the low solubility of L1 in aqueous medium, which would be deleterious for the interaction with the tetrameric complex [CuI(PPh3)]4.

With an optimized catalytic system in hand (Table 2, entry 4), we next investigated the potential scope of reactants for this one-pot ultrasonic approach by CuAAC reactions under very mild conditions (Scheme 4). In all cases, the 1,4-disubstituted 1,2,3-triazoles 4a−l were obtained in high conversions (up to 99%) and good yields (up to 93%) after a simple purification process, showing a broad scope and high tolerance of functional groups in aqueous media. As expected, benzyl bromide (1a) and p-chlorobenzyl iodide (1c) reacted very well, providing triazoles 4a and 4c in 90−93% yields, whereas the same triazole 4a was obtained in 75% yield with the unreactive benzyl chloride (1b). No loss of efficacy was observed for p-fluorophenylacetylene, leading to the product 4b in a good yield. The next step to show reaction generality was exploring the terminal alkynes hydroxyarene derivatives 3e−g to give the expected triazoles 4d−f in 88−93% yields. From these aryloxy-triazoles, both naphthyl- and coumarin-substituted 4e−f could be promising fluorophores in photophysical applications; indeed, coumarin derivatives have been applied as fluorescent probes to metal-ion sensing and visualize the metabolism of cysteine in cells41,42 (Scheme 4).

Table 3. Ligand Effects for the One-Pot US-Assisted Model Reaction

| entry | PPh3 (mol %) | L1 (mol %) | conv (%) |
|-------|-------------|------------|----------|
| 1a    | 10          | 10         | 96       |
| 2a    | 10          | 10         | 95       |
| 3a    | 10          | 10         | 95       |
| 4d    | 71          | 10−30      | 83−86    |
| 5d    | 30          | 83         |

*Reaction conditions: equimolar amounts (0.50 mmol) of 1a−e, 2, and 3a−h, and catalyst (1 mol %) in 2.0 mL of water under USI (20 kHz, 300 W) at 60 °C for 30 min. Reaction run with benzyl bromide (1a). Reaction run with benzyl chloride (1b). Reaction run with 4-chlorobenzyl iodide. Reaction run with 1.0 mmol of 1a. Reaction run with 1,3-bis(bromomethyl)-5-methylbenzene (1d), 2 (1.0 mmol), and phenylacetylene (3a, 1.0 mmol). Reaction run with 2,6-bis(chloromethyl)pyridine (1c), 2 (1.0 mmol), and 3a (1.0 mmol).
Importantly, by XRC, we carried out a full structural analysis aiming to obtained complexes was studied and their structures were solved enhanced. compound, as well as other possible applications, would be biological e can be converted into an amine functional group. Therefore, the resulted in a slight increase in the yield of (Scheme 4) to 0.50 mol % (Scheme 5). Increasing the scale also over, the overall catalyst loading was decreased from 1.0 rendering our developed methodology an ideal multicomponent process with the formation of six covalent bonds. In a more challenging version of this approach, 1,3-bis(bromomethyl)-5-methyl-benzene (1d) and 2,6-bis(chloromethyl)pyridine (1e) provided the bis-triazoles 4j–l in good yields by a pseudo-five-component process with the formation of six covalent bonds. Curiously, the 2,6-bis(triazolyl)pyridine 4l could be used as an N-heterocyclic ligand for the preparation of coordination complexes and/or for metal-ion sensing (Scheme 4).

The ultrasound-assisted multicomponent synthesis developed in this work was distinguished by its regiospecificity, low catalyst loading (1 mol %), compatibility with oxygen/water, broad substrate scope, operational simplicity, reduced reaction times, high atom economy, and environmental friendliness. Pleasingly, this protocol fulfills at least 8 out of the 12 principles of green chemistry, including (1) prevention, (2) atom economy, (3) less hazardous chemical syntheses, (4) safer solvents and auxiliaries, (5) energy-efficient design, (6) reduced derivatives, (7) catalysis, and (8) inherently safer chemistry for accident prevention. It should be noted that although the yields of the 1,2,3-triazoles obtained in this work are comparable to those already reported in the literature, the new Cu(I) complex under ultrasonic conditions dramatically decrease reaction time from hours to minutes. Moreover, this approach provides products in pure form by the formation of three bonds in one step and without the need of large quantities of copper source and any kind of additive or organic co-solvent rendering our developed methodology an ideal multicomponent click reaction.

At this stage of our investigation, we decided to run the click reaction under ultrasound on a 7 g scale to obtain a key product for potential later synthetic applications. Scalability was tested in the benzyl bromide (1b, 25 mmol scale) reaction with the terminal alkyne 3e and sodium azide (2) to afford the product 4d. Analytically pure 1,2,3-triazole 4d (6.982 g) was obtained without requiring column chromatography purification. Moreover, the overall catalyst loading was decreased from 1.0 (Scheme 4) to 0.50 mol % (Scheme 5). Increasing the scale also resulted in a slight increase in the yield of 4d from 88 to 90%. Importantly, N-benzyl-1,2,3-triazole 4d containing a nitro group can be converted into an amine functional group. Therefore, the biological effect of such post-functionalized 1,2,3-triazole-based compound, as well as other possible applications, would be enhanced.

As part of this study, since the catalytic activity of the two obtained complexes was studied and their structures were solved by XRC, we carried out a full structural analysis aiming to find a relationship between these results. Complexes [CuPPh3]4 and CuL1PPh3 crystallize in the monoclinic I2/c and triclinic P-1 space groups as tetra- and mononuclear molecules, respectively. Cu(I) describes tetrahedral coordination geometries in both complexes, though an unusual trigonal planar geometry is observed in [CuPPh3]4 allowing a metal–metal bonding interaction between Cu atoms. Despite the differences in the molecular structures, bond distances of Cu–P (∼2.2 Å) and Cu–I (∼2.5–2.7 Å) are similar. In the supramolecular structure, no classic hydrogen bonds were found causing that only van der Waals forces are involved in the three-dimensional structure. Crystallographic data and a deeper description of the crystal structures are provided in the SI. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of FMO (frontier molecular orbital) energy levels for complexes were computed from the crystallographic results (Scheme 6), and thus we managed to find a notable correlation with their catalytic properties (see the SI for details).

The calculations were carried out by the STO-3G basis set at the Hartree–Fock level theory.

The calculations were carried out by the STO-3G basis set at the Hartree–Fock level theory executed in CrystalExplorer using the crystallographic information files (.cif) obtained from the X-ray diffraction measurements. These FMO results show that the new complex has stronger hardness than [CuPPh3]4, with HOMO–LUMO energy gap values of 7.14 and 2.56 eV,
respectively. Likewise, both FMOs of CuIL1PPh3 exhibit a greater metal character than those of the tetrameric complex; indeed, the LUMO of mononuclear complex has a very strong metal character mostly located around the copper atom, and thus, this complex is more electrophilic. Consequently, the interaction between reagents and the catalyst in the Cu(I)-mediated click reaction to form the 1,2,3-triazoles 4a–I could be more favored with the new complex (see Table 3 and Scheme 6). Probably, these findings clarify the high catalytic activity of CuIL1PPh3 in the US-assisted click reaction studied by us, which is predominantly governed by both electrostatic interactions and steric effects (see the SI for more details).

■ CONCLUSIONS

In summary, we have synthesized a new Cu(I) complex bearing bis(3,5-dimethyl-1H-pyrazol-1-yl)methane and PPh3 ligands that served as an effective catalyst to obtain 1,4-disubstituted 1,2,3-triazoles in yields up to 93%. This complex type is scarce, but was prepared using readily available reagents, and could be successfully handled in air and water without any particular precautions. Gratifyingly, the structure of CuIL1PPh3 complex was confirmed by XRC analysis; in addition, we managed to find a key connection with its high catalytic activity using the CE-HF model. As far as we know, this is the first report of using an ultrasone homogenizer combined with a coordination complex in the synthesis of triazoles via a three-component click reaction from an alkyl halide, sodium azide, and terminal alkyne in the synthesis of triazoles via a three-component click reaction.

This synthetic methodology is simple and efficient to prepare functionalized triazoles, and the results found are evidence that the economical and easily accessible CuIL1PPh3 complex could assist the possibility for the widespread demand. Likewise, its application allows significant advantages including high atom economy, low catalyst loading, environmental friendliness, broad substrate scope under exceedingly mild reaction condition, high yield, shorter reaction time, operational simplicity, reduced alkene–alkyne homocoupling products, and handling of volatile alkynes and unstable organic azides in air and water. In addition, triazoles bearing pyridine, naphthalene, and coumarin could be used in the design of fluorescent probes for species sensing of biomedical and environmental interest, among other applications. Ultimately, an effective scalable sequence to obtain a nitro-substituted triazole has been developed.

■ EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without further purification. All starting materials were weighed and handled in air at room temperature. Progression of reactions and purifications of products were monitored by thin-layer chromatography (TLC) on silica gel (60 F254) using UV light as a visualization agent. Silica gel (230–400 mesh) was used for flash chromatography. Ultrasound-assisted reactions were performed using an ultrasonic Sonics Vibra-Cell VCX 750 probe equipped with both a tapered micro-tip of 1/4″ and a thermocouple. Reactions under ultrasound were performed using a 25 mL glass vial, and the resulting reaction mixture was stirred at room temperature for 12 h. Then, the reaction mixture was filtered, and the solid residue was recrystallized from acetonitrile to afford the pure CuIL1PPh3 complex as a white solid (98.1 mg, 54%); mp 192–194 °C (amorphous). Crystals suitable for X-ray structure analysis for complex CuIL1PPh3 were obtained from acetonitrile by slow evaporation of the solution at room temperature. The noncommercially available alkynes 3e–h were prepared by a method developed in our laboratory.

Synthesis and Characterization. Synthesis of CuIL1PPh3 Complex. A mixture of 2 equiv of bis(3,5-dimethyl-1H-pyrazol-1-yl)methane (L1), 114 mg, 0.56 mmol) in dichloromethane (5.0 mL) was added to a suspension with 1.0 equiv of Cu(I) (129 mg, 0.28 mmol) from precursor [CuPPh3]4 in the same solvent (7.0 mL). The resulting mixture was stirred at 40 °C for 2 h, after which the reaction mixture was cooled to room temperature. Subsequently, the suspension was filtered, the filtrate was dried under reduced pressure, and the solid residue was recrystallized from acetonitrile to afford the pure CuIL1PPh3 complex as a white solid (98.1 mg, 54%); mp 192–194 °C (amorphous). Crystals suitable for X-ray structure analysis for complex CuIL1PPh3 were obtained from acetonitrile by slow evaporation of the solution at room temperature (see the SI for details). FTIR (KBr): 420, 497, 694, 740, 1096, 1284, 1431, 1558, 1587, 2923, 3010, 3054 cm–1. The ligand bis(3,5-dimethyl-1H-pyrazol-1-yl)methane (L1)32 and the precursor complex [CuPPh3]4 were synthesized as described in the literature. Crystals suitable for X-ray structure analysis of [CuPPh3]4 were obtained from acetonitrile by slow evaporation of the solution at room temperature. The noncommercially available alkynes 3e–h were prepared by a method developed in our laboratory.

General Procedure for the Synthesis of Terminal Alkynes 3e–h. An equimolar mixture (6.77 mmol) of cesium carbonate (Cs2CO3, 2.2 g) and the respective nucelophile 5a–d in anhydrous DMF (5.0 mL) was stirred at room temperature for 30 min. To this white suspension was added the propargyl bromide solution 80 wt % in toluene (6, 754 μL) in one portion, and the resulting reaction mixture was stirred at room temperature for 12 h. Then, the reaction mixture was filtered and rinsed with ethyl acetate (3 × 10.0 mL). The combined organic layers were washed with brine (3 × 10.0 mL), dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash...
chromatography on silica gel (eluents: CH₂Cl₂) to afford the pure terminal alkyne 3e–h, which were identified by comparison of its spectroscopic data with those reported in the literature.

1-Nitro-4-(prop-2-yn-1-yloxy)benzene (3e). Following the general procedure, the reaction of 4-nitrophenol (5a, 942 mg, 6.77 mmol), propargyl bromide in toluene (6, 754 μL, 6.77 mmol), and Cs₂CO₃ (2206 mg, 6.77 mmol) in 5.0 mL of anhydrous DMF at 25 °C for 12 h afforded compound 3e as a yellow solid (1055 mg, 88%); mp 119–120 °C (ref60, 118–119 °C). ¹H NMR (400 MHz, CDCl₃): δ = 2.59 (t, J = 2.4 Hz, 1H), 4.80 (d, J = 2.4 Hz, 2H), 7.06 (d, J = 9.2 Hz, 2H), 8.23 (d, J = 9.2 Hz, 2H) ppm. ¹³C{¹H} NMR (101 MHz, CDCl₃): δ = 56.3 (CH₂), 76.8 (CH), 77.12 (C), 115.0 (CH), 125.9 (CH), 142.1 (C), 162.3 (C) ppm. HRMS (ESI+): calc for C₉H₇NO₃⁺ 178.0499 [M + H⁺]; found 178.0498. These NMR data matched previously reported data.⁵⁰

2-(Prop-2-yn-1-yloxy)naphthalene (3f). Following the general procedure, the reaction of 2-naphthol (5b, 976 mg, 6.77 mmol), propargyl bromide in toluene (6, 754 μL, 6.77 mmol), and Cs₂CO₃ (2206 mg, 6.77 mmol) in 5.0 mL of anhydrous DMF at 25 °C for 12 h afforded compound 3f as a brown solid (1036 mg, 84%); mp 60–62 °C (ref61, 48–50 °C). ¹H NMR (400 MHz, CDCl₃): δ = 2.55 (t, J = 2.4 Hz, 1H), 4.79 (d, J = 2.4 Hz, 2H), 7.18 (dd, J = 3.0, 8.2 Hz, 1H), 7.23 (d, J = 5.6 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5, 1H), 7.74–7.78 (m, 3H) ppm. ¹³C{¹H} NMR (101 MHz, CDCl₃): δ = 55.8 (CH₂), 75.7 (CH), 78.5 (C), 107.4 (CH), 118.7 (CH), 124.0 (CH), 126.5 (CH), 126.9 (CH), 127.7 (CH), 129.3 (C), 129.6 (CH), 134.3 (C), 155.4 (C) ppm. HRMS (ESI+): calc for C₁₅H₁₄NO₂⁺ 236.1182 [M + H⁺]; found 236.1188. These NMR data matched previously reported data.⁵⁰

7-(Prop-2-yn-1-yloxy)-2H-chromen-2-one (3g). Following the general procedure, the reaction of 7-hydroxycumarin (5c, 1098 mg, 6.77 mmol), propargyl bromide in toluene (6, 754 μL, 6.77 mmol), and Cs₂CO₃ (2206 mg, 6.77 mmol) in 5.0 mL of anhydrous DMF at 25 °C for 12 h afforded compound 3g as a white solid (989 mg, 73%); mp 125–126 °C (ref47, 120–126 °C). ¹H NMR (400 MHz, CDCl₃): δ = 2.55 (t, J = 2.4 Hz, 1H), 4.76 (d, J = 2.4 Hz, 2H), 6.28 (d, J = 9.2 Hz, 1H), 6.90–6.94 (m, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 9.6 Hz, 1H) ppm. ¹³C{¹H} NMR (101 MHz, CDCl₃): δ = 56.2 (CH₂), 76.6 (CH), 77.4 (C), 102.1 (CH), 113.1 (CH), 113.2 (C), 113.6 (CH), 128.8 (CH), 143.3 (CH), 155.6 (CH), 160.5 (CH), 161.0 (C) ppm. HRMS (ESI+): calc for C₁₅H₁₄ NO₃⁺ 283.1051 [M + H⁺]; found 283.1050. These NMR data matched previously reported data.⁵¹

N-Benzyl-prop-2-yn-1-amine (3h). Following the general procedure, the reaction of benzylamine (5d, 1474 μL, 13.50 mmol), propargyl bromide in toluene (6, 754 μL, 6.77 mmol), and Cs₂CO₃ (2206 mg, 6.77 mmol) in 5.0 mL of anhydrous DMF at 25 °C for 12 h afforded compound 3h as a colorless oil (698 mg, 71%). ¹H NMR (400 MHz, CDCl₃): δ = 2.26 (t, J = 2.4 Hz, 1H), 3.42 (d, J = 2.4 Hz, 2H), 3.88 (s, 2H), 7.23–7.36 (m, 5H) ppm. ¹³C{¹H} NMR (101 MHz, CDCl₃): δ = 37.3 (CH₃), 52.3 (CH₂), 71.6 (CH), 82.0 (C), 127.2 (CH), 128.4 (CH), 128.5 (CH), 139.4 (C) ppm. HRMS (ESI+): calc for C₁₉H₁₆N₂O⁺ 291.1139 [M + H⁺]; found 291.1136. These NMR data matched previously reported data.⁵¹

General Procedure for the Synthesis of 1,2,3-Triazoles 1,4-Disubstituted 4a–l. A mixture of the aldehyde halide 1 (0.50 mmol), sodium azide (2, NaN₃, 0.50 mmol), terminal alkene 3 (0.50 mmol), and Cu(II)PPh₃ complex (3.3 mg, 1 mol %) afforded compound 4d as a yellow pale solid (136 mg, 88%); mp 103–104 °C (ref48, 94–96 °C). ¹H NMR (400 MHz, CDCl₃): δ = 5.27 (s, 2H), 5.55 (s, 2H), 7.05 (d, J = 9.2 Hz, 2H), 7.27–7.30 (m, 2H), 7.38–7.41 (m, 3H), 7.56 (s, 1H), 8.19 (d, J = 9.2 Hz, 2H) ppm. ¹³C{¹H} NMR (101 MHz, CDCl₃): δ = 54.4 (CH₂), 62.4 (CH₂), 114.8 (CH), 123.0 (CH), 125.9 (CH), 128.2 (CH), 128.3 (CH), 129.2 (CH), 134.2 (C), 141.9 (C), 143.2 (C), 163.1 (C) ppm. HRMS (ESI+): calc for C₁₆H₁₅N₃O₄⁺ 311.1139 [M + H⁺];
found 311.1143. These NMR data matched previously reported data.\(^{48}\)

1-Benzyl-4-((napthalen-2-yl oxy)methyl)-1H-1,2,3-triazole (4e). The general procedure at 60 °C for 30 min between benzyl bromide 1a (59 µL, 0.50 mmol), sodium azide (2, 32 mg, 0.50 mmol), 2-prop-2-yloxy naphthalene \((3f, 91 \text{ mg}, 0.50 \text{ mmol})\), and \( \text{CuI L1PPh}_{3} \) (3.3 mg, 1 mol %) afforded compound 4e as a white solid (160 mg, 87%); mp 83–85 °C. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.59 \) (s, 4H), 3.74 (s, 2H), 5.52 (s, 2H), 7.20–7.40 (m, 16H) ppm. \(^{13}C\)\(^{1}H\) NMR (101 MHz, CDCl\(_3\)): \( \delta = 48.2 \) (CH\(_2\)), 54.0 (CH\(_2\)), 57.7 (CH\(_2\)), 122.4 (CH), 126.9 (CH), 127.8 (CH), 128.2 (CH), 128.8 (CH), 129.1 (CH), 134.9 (C), 139.2 (C), 146.0 (C) ppm. HRMS (ESI\(^{+}\))+: calcd for C\(_{23}H\(_{22}N\(_{6}\)O\(_{2}\)) 369.2074 [M + H\(^{+}\)]; found 369.2072.

1-(5-Methyl-1,3-phenylene)bis(methylene)bis(4-phenyl-1H,1,2,3-triazole) (4f). The general procedure at 60 °C for 30 min between 1,3-bis(bromomethyl)-5-methylbenzene 1d (139 mg, 0.50 mmol), sodium azide (2, 66 mg, 1.01 mmol), ethynylbenzene 3a (115 µL, 1.05 mmol), and \( \text{CuI L1PPh}_{3} \) (3.3 mg, 1 mol %) afforded compound 4f as a white solid (173 mg, 85%); mp 159–160 °C (ref\(^{51}\), 145–146 °C). \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta = 2.31 \) (s, 3H), 5.50 (s, 4H), 7.06–7.08 (m, 3H), 7.31 (t, \( J = 7.4 \) Hz, 2H), 7.39 (t, \( J = 7.4 \) Hz, 4H), 7.68 (s, 2H), 7.79 (d, \( J = 7.4 \) Hz, 4H) ppm. \(^{13}C\)\(^{1}H\) NMR (101 MHz, CDCl\(_3\)): \( \delta = 21.3 \) (CH\(_2\)), 35.9 (CH\(_2\)), 119.7 (CH), 124.6 (CH), 125.8 (CH), 128.3 (CH), 128.9 (CH), 129.1 (CH), 130.5 (C), 135.9 (C), 140.3 (C), 148.4 (C) ppm. HRMS (ESI\(^{+}\))+: calcd for C\(_{34}H\(_{26}N\(_{10}\)O\(_{2}\)) 407.1979 [M + H\(^{+}\)]; found 407.1980. These NMR data matched previously reported data.\(^{51}\)

In Supporting Information, \( \text{Supporting Information} \), copies of \( ^{1}H \) and \( ^{13}C\)\(^{1}H\) NMR spectra for all compounds and crystallographic details of Cu(I) complexes (PDF) are available.
CuIL1PPh3 (CIF)

Accession Codes
CCDC 2010534 (CuIL1PPh3) and 201053 ([CuI(PPh3)3]_4) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge through www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK;fax:+44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors
John Hurtado —Grupo de Investigación en Química Inorgánica, Catálisis y Bioinorgánica, Department of Chemistry, Universidad de los Andes, Bogotá 111711, Colombia; orcid.org/0000-0002-0511-9719; Email: jj.hurtado@uniandes.edu.co
Jaime Portilla —Bioorganic Compounds Research Group, Department of Chemistry, Universidad de los Andes, 111711 Bogotá, Colombia; orcid.org/0000-0002-8206-7481; Email: jportill@uniandes.edu.co

Authors
Juan-Carlos Castillo —Bioorganic Compounds Research Group, Department of Chemistry, Universidad de los Andes, 111711 Bogotá, Colombia; Escuela de Ciencias Química, Universidad Pedagógica y Tecnológica de Colombia, Tunja 150003, Colombia
Nestor-Fabian Bravo —Bioorganic Compounds Research Group, Department of Chemistry, Universidad de los Andes, 111711 Bogotá, Colombia
Lenka-Victoria Tamayo —Grupo de Investigación en Química Inorgánica, Catálisis y Bioinorgánica, Department of Chemistry, Universidad de los Andes, Bogotá 111711, Colombia
Paula-Daniela Mestizo —Grupo de Investigación en Química Inorgánica, Catálisis y Bioinorgánica, Department of Chemistry, Universidad de los Andes, Bogotá 111711, Colombia
Mario Macías —Department of Chemistry, Universidad de los Andes, Bogotá 111711, Colombia
Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c04592

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the Chemistry Department and Vicerrectoría de Investigaciones at the Universidad de Los Andes for financial support. J.H. and J.P. acknowledge support from the Science Faculty (projects INV-2018-50-1354 and INV-2019-84-1800, respectively). J.-C.C. thanks the Dirección de Investigaciones at the Universidad Pedagógica y Tecnológica de Colombia (project SGI-2829). The authors also acknowledge Sandra Ortiz for acquiring the mass spectra.

■ REFERENCES

(1) Tabasso, S.; Camaroglio, D.; Calcio, E.; Cravotto, G. Microwave, ultrasound and ball mill procedures for bio-waste valorisation. Green Chem. 2015, 17, 684—693.
(2) Pinedo, M. Microwave and mecanochemistry: Tools for the sustainable. Targets Heterocycl. Syst. 2016, 20, 197—221.
(3) Baig, R. B.; Varma, R. S. Alternative energy input: mecanochemical, microwave and ultrasound-assisted organic synthesis. Chem. Soc. Rev. 2012, 41, 1559—1584.
(4) Banerjee, B. Recent developments on ultrasound assisted catalyst-free organic synthesis. Ultrason. Sonochem. 2017, 35, 1—14.
(5) Chemat, F.; Rombaut, N.; Sicaire, A.-G.; Meulemiste, A.; Fabiano-Tixier, A.-S.; Abert-Vian, M. Ultrasound assisted extraction of food and natural products. Mechanisms, techniques, combinations, protocols and applications. Ultrason. Sonochem. Ultrason. Sonochem. 2017, 34, 540—560.
(6) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective “ligation” of azides and terminal alkynes. Angew. Chem. Int. Ed. 2002, 41, 2596—2599.
(7) Torrón, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. J. Org. Chem. 2002, 67, 3057—3064.
(8) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click chemistry: diverse chemical function from a few good reactions. Angew. Chem., Int. Ed. 2001, 40, 2004—2021.
(9) Insuasty, D.; Castillo, J.; Becerra, D.; Rojas, H.; Abonia, R. Synthesis of biologically active molecules through multicomponent reactions. Molecules 2020, 25, 505.
(10) Liu, E.-C.; Topczewski, J. T. Enantioselective copper catalyzed alkyne—azide cycloaddition by dynamic kinetic resolution. J. Am. Chem. Soc. 2019, 141, 5135—5138.
(11) Li, Z.; Shao, S.; Ren, X.; Sun, J.; Guo, Z.; Wang, S.; Song, M. M.; Chang, C. A.; Xue, M. Construction of a sequenceable protein mimetic peptide library with a true 3D diversifiable chemical space. J. Am. Chem. Soc. 2018, 140, 14552—14556.
(12) Chen, J.; Wang, J.; Li, K.; Wang, Y.; Gruebele, M.; Ferguson, A. L.; Zimmerman, S. C. Polymeric “clickase” accelerates the copper click reaction of small molecules, proteins, and cells. J. Am. Chem. Soc. 2019, 141, 9693—9700.
(13) Döhler, D.; Michael, P.; Binder, W. H. CuAAC-based click chemistry in self-healing polymers. Acc. Chem. Res. 2017, 50, 2610—2620.
(14) Fu, F.; Martinez, A.; Wang, C.; Ciganda, R.; Yate, L.; Escobar, A.; Moya, S.; Fouquet, E.; Ruiz, J.; Astruc, D. A copper-II metal—organic hydrogel as a multifunctional precatalyst for CuAAC reactions and chemical fixation of CO₂ under solvent-free conditions. Chem. Commun. 2017, 53, 5384—5387.
(15) Li, M.; Zheng, N.; Li, J.; Zheng, Y.; Song, W. Iridium-catalyzed orthogonal and regioselective synthesis of triazole disulfides in aqueous media under mild conditions. Green Chem. 2020, 22, 2394—2398.
(16) Meng, J.-C.; Fokin, V. V.; Finn, M. G. Kinetic resolution by copper-catalyzed azide—alkyne cycloaddition. Tetrahedron Lett. 2005, 46, 4543—4546.
(17) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. Polytriazoles as copper(II)-stabilizing ligands in catalysis. Org. Lett. 2004, 6, 2853—2855.
(18) Yin, Z.; Comellas-Aragones, M.; Chowdhury, S.; Bentley, P.; Kaczanowska, K.; BenMohamed, L.; Gildersleeve, J. C.; Finn, M. G.; Huang, X. Boosting immunity to small tumor-associated carbohydrates with bacteriophage Q₅₁-capsids. ACS Chem. Biol. 2013, 8, 1253—1262.
(19) Oxikal, E.; Llanes, P.; Bravo, F.; Ferrali, A.; Pericas, M. A. Fine-tunable tris(triazolyl)methane ligands for copper(I)-catalyzed azide—alkyne cycloaddition reactions. ChemInform 45. DOI: 10.1002/chin.201435152.
(20) Pérez-Baldarés, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asin, J. A.; Isaac-García, J.; Santoyo-González, F. Multivalent neoglycoconjugates by regiospecific cycloaddition of azides and alkynes using organic-soluble copper catalysts. Org. Lett. 2003, 5, 1951—1954.
(21) Wang, D.; Li, N.; Zhao, M.; Shi, W.; Ma, C.; Chen, B. Solvent-free synthesis of 1,4-disubstituted 1,2,3-triazoles using a low amount of Cu(PPh₃)₂NO₃ complex. Green Chem. 2010, 12, 2120–2123.

(22) Lal, S.; McNally, J.; White, A. J. P.; Diez-González, S. Novel phosphinite and phosphonite copper(I) complexes: efficient catalysts for click azide–alkyne cycloaddition reactions. Organometallics 2011, 30, 6225–6232.

(23) Nunéz-Dallos, N.; Muñoz-Castro, A.; Fuentelba, M.; Pérez, E. G.; Hurtado, J. Facile synthesis of a luminescent copper(I) coordination polymer containing a flexible benzotriazole-based ligand: An effective catalyst for three-component azide-alkyne cycloaddition. Inorg. Chem. Acta 2019, 498, No. 191136.

(24) Kappe, C. O.; Van der Eycken, E. Click chemistry under non-classical reaction conditions. Chem. Soc. Rev. 2010, 39, 1280–1290.

(25) Sreedhar, B.; Reddy, P. S. Sonochemical synthesis of 1,4-disubstituted 1,2,3-triazoles in aqueous medium. Synth. Commun. 2007, 37, 805–812.

(26) Mady, M. F.; Awad, G. E. A.; Jørgensen, K. B. Ultrasound-assisted synthesis of novel 1,2,3-triazoles coupled diaryl sulfone moieties by the CuAAC reaction, and biological evaluation of them as antioxidant and antimicrobial agents. Eur. J. Med. Chem. 2014, 84, 433–443.

(27) Rezki, N.; Aoud, M. R. Green ultrasound-assisted three-component click synthesis of novel 1H-1,2,3-triazole carrying benzothiazoles and fluorinated-1,2,4-triazole conjugates and their antimicrobial evaluation. Acta Pharm. 2017, 67, 309–324.

(28) Naeimi, H.; Dadashzadeh, S.; Moradian, M. Facile and efficient sonochemical synthesis of 1,4-disubstituted 1,2,3-triazole derivatives catalyzed by Cu under mild conditions. Res. Chem. Intermed. 2015, 41, 2687–2695.

(29) Vargas-Oviedo, D.; Butassi, E.; Zacchino, S.; Portilla, J. Eco-friendly synthesis and antibacterial evaluation of N-substituted benzimidazoles. Monatsh. Chem. 2020, 151, 575–588.

(30) Castillo, J.-C.; Portilla, J. Recent advances in the synthesis of new pyrazole derivatives. Targets Heterocycl. Syst. 2018, 22, 194–223.

(31) Tigeros, A.; Macías, M.; Portilla, J. Photophysical and crystallographic study of three integrated pyrazolo[1,5-a]pyrimidine–triphenylamino systems. Dyes Pigments 2021, 184, No. 108730.

(32) Zhang, Z.; Cui, D.; Trifonov, A. A. Synthesis and characterization of heteroscorpionate rare-earth metal dialkyl complexes and catalysis on MMA polymerization. Eur. J. Inorg. Chem. 2010, 18, 2861–2866.

(33) Fife, D. J.; Moore, W. M.; Morse, K. W. Solution equilibria of N-heterocyclic carbene or phosphine-copper(I) complexes with neutral N₄ tripodal ligands: Influence of the number of Mg²⁺ by a new fluorescent naphthyl bearing 1,2,3-triazole moieties. CrystalExplorer17 2018, 8, 7889–7897.

(34) Orrego-Hernández, J.; Muñoz-Dallos, N.; Portilla, J. Recognition of Mg²⁺ by a new fluorescent “turn-on” chemosensor based on pyridyl-hydrazono-coumarin. Talanta 2016, 152, 432–437.

(35) Wang, D.; Li, N.; Zhao, M.; Shi, W.; Ma, C.; Chen, B. Solvent-free synthesis of 1,4-disubstituted 1,2,3-triazoles using a low amount of Cu(PPh₃)₂NO₃ complex. Green Chem. 2010, 12, 2120–2123.

(36) Tsigkis, N.; Mørup, M. G.; Hurtado, J. Facile synthesis of a luminescent copper(I) coordination polymer containing a flexible benzotriazole-based ligand: An effective catalyst for three-component azide-alkyne cycloaddition. Inorg. Chem. Acta 2019, 498, No. 191136.

(37) Kappe, C. O.; Van der Eycken, E. Click chemistry under non-classical reaction conditions. Chem. Soc. Rev. 2010, 39, 1280–1290.

(38) Sreedhar, B.; Reddy, P. S. Sonochemical synthesis of 1,4-disubstituted 1,2,3-triazole derivatives catalyzed by Cu under mild conditions. Res. Chem. Intermed. 2015, 41, 2687–2695.

(39) Vargas-Oviedo, D.; Butassi, E.; Zacchino, S.; Portilla, J. Eco-friendly synthesis and antibacterial evaluation of N-substituted benzimidazoles. Monatsh. Chem. 2020, 151, 575–588.

(40) Castillo, J.-C.; Portilla, J. Recent advances in the synthesis of new pyrazole derivatives. Targets Heterocycl. Syst. 2018, 22, 194–223.

(41) Tigeros, A.; Macías, M.; Portilla, J. Photophysical and crystallographic study of three integrated pyrazolo[1,5-a]pyrimidine–triphenylamino systems. Dyes Pigments 2021, 184, No. 108730.

(42) Tigeros, A.; Portilla, J. Recent progress in chemosensors based on pyrazole derivatives. RSC Adv. 2020, 10, 19693–19712.
analogs as antiplasmodial agents, cytotoxicity and docking studies. Bioorg. Med. Chem. 2017, 25, 221−232.

(62) Ferraroni, M.; Carta, F.; Scozzafava, A.; Supuran, C. T. Thioxocoumarins Show an Alternative Carbonic Anhydrase Inhibition Mechanism Compared to Coumarins. J. Med. Chem. 2016, 59, 462−473.