Received: 6 November 2020 | Revised: 26 December 2020 | Accepted: 17 January 2021

DOI: 10.1002/aoc.6180

FULL PAPER

Applied Organometallic Chemistry WILEY

Heterocyclic thiolates and phosphine ligands in copper-catalyzed synthesis of propargylamines in water

Abdollah Neshat[1] | **Mohammad Gholinejad**[1] | **Mahmoud Afrasi**[1] | **Piero Mastrorilli**[2] | **Stefano Todisco**[2] | **Shirin Gilanchi**[1] | **Farzane Osanlou**[1]

[1]Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Zanjan, Iran

[2]DICATECh Department Politecnico di Bari, Bari, Italy

Correspondence
Abdollah Neshat, Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Zanjan 45137-66731, Iran.
Email: a.neshat@iasbs.ac.ir

Funding information
Institute for Advanced Studies in Basic Sciences (IASBS) Research Council

The product obtained by reaction of deprotonation of 2-mercaptobenzothiazole or methimazole (2-mercapto-1-methylimidazole) with copper iodide in the presence of tertiary phosphines, PR_2R' (R = R′ = cyclohexyl; R = R′ = phenyl; R = phenyl, R′ = methyl) showed high catalytic activity in A^3 coupling of a series of aldehydes with phenylacetylene and piperidine, yielding propargylamines. An investigation into the nature of active species carried out mainly by electrospray ionization mass spectrometry (ESI-MS) techniques underscores a crucial role played by organosulfur and organophosphorus compounds in the generation of active species responsible for these reactions. The coupling reactions were successfully carried out at low catalyst loadings in water/THF (20:1) and in relatively short reaction times. The scope of the reaction was also investigated with 20 examples.

KEYWORDS
2-mercaptobenzothiazole, A^3 coupling, catalysis, methimazole, propargylamines

1 | INTRODUCTION

Propargylamines are important compounds in the synthesis of pharmaceutical and natural products, particularly in the treatment of Alzheimer's and Parkinson's diseases.[1] Classic methods for the synthesis of propargylamines utilized stoichiometric reaction of lithium acetylides or Grignard reagents with imine derivatives that required inert atmosphere and dry solvents.[2] Currently, an atom-economic and efficient pathway for the preparation of propargylamines is transition metal catalyzed coupling of aldehydes with alkynes and amines, which is commonly known as A^3 coupling reactions.[3] Silver chloride salt or silver nanoparticles in combination with tertiary phosphines is a well-established method to efficiently catalyze A3 coupling reactions in water.[4–22] Progress in the synthesis of highly ordered mesoporous organic polymers has allowed their surface decoration with transitions metal ions via grafting techniques.[23,24] Transition metal ion-grafted mesoporous organic polymers were utilized by various groups as efficient catalysts in the multicomponent coupling reactions. Grafting techniques in these systems have allowed efficient recoverability and reusability of catalysts for several reactions runs. Besides, the polar nature of these catalysts has also allowed carrying out catalytic reactions in an aqueous media.[25–27]

Efficient catalysts based on N-heterocyclic carbene complexes of coinage metals have been developed during past few years.[28–37] Copper-based catalysts because of natural abundance of copper metal and high reactivity have also attracted great attention.[38]

In our quest to develop a novel and highly efficient homogeneous catalytic system based on copper, we observed that mixing copper iodide with deprotonated

2-mercaptobenzothiazole or 2-mercapto-1-methylimidazole (methimazole), in the presence of monodentate tertiary phosphines, afforded efficient catalyst precursors for the synthesis of propargylamines via A^3-coupling reactions.

Previous reports dealing with complexes of copper ions with phosphine and neutral heterocyclic thiones revealed that in the majority of these compounds, heterocyclic thiones prefer a monodentate binding mode, coordinating exclusively through exocyclic sulfur atom.[39–43] Due to soft nature of sulfur atom in heterocyclic thiones, we speculated that copper–phosphine complexes with thiolates would provide interesting mixed-ligand coordination complexes, suitable for certain catalytic reactions. Structural characterization of a catalytic system is an important step in aiming at mechanistic understanding of a catalytic process. Therefore, we set out to explore true nature of main species under "operando"-conditions, identical to the conditions of the catalytic application. In our employed synthetic route, the expected metal complexes comprising both phosphine and thionate ligands were formed in small quantity. However, the investigation of true nature of catalyst revealed that copper (I) phosphine and Cu (II) thiolates are highly active catalysts in A^3 coupling reactions even in water at room temperature (rt) reactions.

2 | EXPERIMENTAL SECTION

2.1 | General considerations

Reagents and solvents were used as received from commercial suppliers. Infrared spectra were recorded on a Bruker Vector 22 Fourier-transform infrared spectroscopy (FT-IR) spectrometer (ATR in the range 400–4,000 cm^{-1}). NMR spectra in solution were recorded on a Bruker AV-400 spectrometer with $SiMe_4$ for ^1H and ^{13}C as external references. High-resolution mass spectrometry (HR-MS) analyses were performed in positive mode using a time-of-flight mass spectrometer equipped with an electrospray ion source (Bruker micrOTOF II). The sample solutions were introduced (as diluted acetonitrile solutions) by continuous infusion with the aid of a syringe pump at a flow rate of 180 μl/h. The instrument was operated at end plate offset −500 V and capillary −4,500 V. The nebulizer pressure was 0.3 bar (N_2) and the drying gas (N_2) flow 4.0 L/min. Capillary exit was 170 V. The drying gas temperature was set at 180°C. The software used for the simulations is Bruker Daltonics Data Analysis (version 4.0). For all described HRMS peaks, the isotopic patterns were superimposable with those calculated on the basis of the proposed formulae.

2.2 | Synthesis of 1–3

2-Mercaptobenzothiazol (100 mg, 0.60 mmol) was dissolved in 5.0 ml of ethanol. Then, potassium hydroxide (33 mg, 0.60 mmol) was added to the flask, and the mixture was stirred for 10 min before the addition of CuI (113 mg, 0.60 mmol). Finally, an appropriate phosphine (tricyclohexylphosphine [167 mg, 0.60 mmol], or methyldiphenylphosphine [110 μl, 0.60 mmol] or triphenylphosphine [156 mg, 0.60 mmol]) was added. After overnight stirring, the resulting orange powder was collected by filtration and dried under nitrogen gas. Yield: 230 mg (mixture **1**), 212 mg (mixture **2**), and 122 mg (mixture **3**).

2.3 | Synthesis of 4–6

Methimazole (100 mg, 0.88 mmol) was dissolved in 5.0-ml ethanol. Then, potassium hydroxide (49 mg, 0.88 mmol) was added to the flask, and the mixture was stirred for 10 min before the addition of CuI (160 mg, 0.88 mmol). Finally, an appropriate phosphine (tricyclohexylphosphine [240 mg, 0.88 mmol], or methyldiphenylphosphine [163 μl, 0.88 mmol] or triphenylphosphine [220 mg, 0.88 mmol]). After overnight stirring, the resulting white solid was collected by filtration and dried under nitrogen gas. Yield: 245 mg (mixture **4**), 232 mg (mixture **5**), and 156 mg (mixture **6**).

2.4 | Synthesis of 10

2-Mercaptobenzothiazole (50 mg, 0.3 mmol) was dissolved in 5.0-ml ethanol. Then, potassium hydroxide (17 mg, 0.3 mmol) was added to the flask, and the mixture was stirred for 10 min before the addition of CuI (56 mg, 0.15 mmol). After 12 h stirring, the resulting yellow solid was collected by filtration and dried under nitrogen gas. Yield: 70 mg, 59%. The same complex could be obtained starting from Cu (II) acetate in methanol.

2.5 | Catalytic runs

To a 5-ml flask containing aldehyde (0.50 mmol), amine (0.75 mmol), phenylacetylene (0.75 mmol) and catalysts (2 mg), and H_2O:THF (10:1, 2 ml) was added, and reaction mixture was stirred for appropriate reaction times at rt. The progress of the reactions was investigated by thin-layer chromatography or ^1H-NMR. After completion of the reaction, the crude product was extracted with ethyl acetate (3 × 5 ml). Subsequent purification was

performed by column or plate chromatography using hexane and ethyl acetate as eluents. All products were characterized by ^{1}H-NMR and ^{13}C-NMR.

2.6 | X-ray crystallography

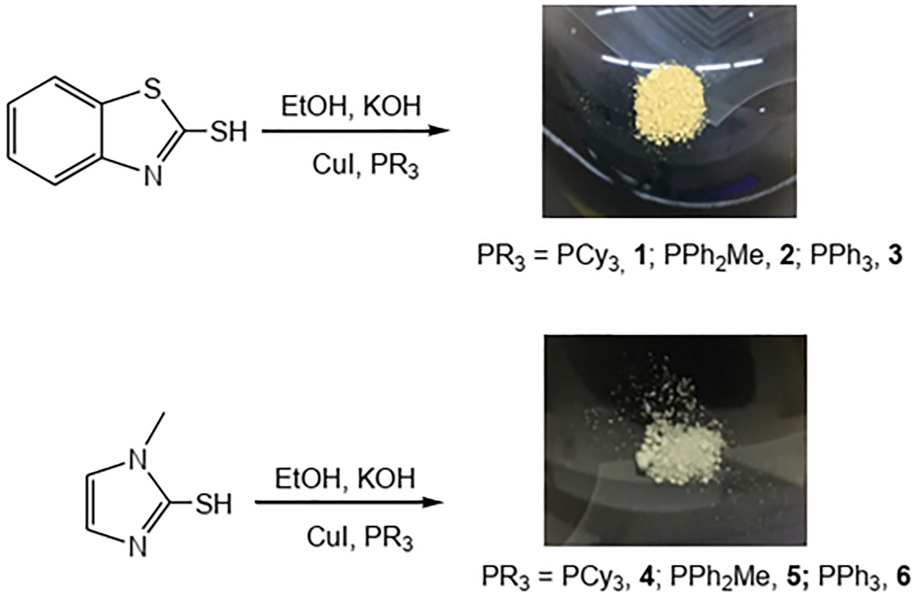
Crystal data and other details of the structure analysis are compiled in Table 3. Diffraction quality crystals of $[(PPh_2Me)_3Cu(I)]$ were obtained by slow evaporation of the solvent from a concentrated acetonitrile solution. Structural determination was performed on a crystal of approximate dimensions 0.3 × 0.3 × 0.2 mm using a STOE IPDS II automated diffractometer equipped with a four-circle Kappa goniometer, an image plate detector, and a monochromatized Mo Kα radiation. The X-ray diffraction (XRD) measurement was carried out on STOE IPDS 2 T diffractometer with graphite-monochromated Mo Kα radiation. Cell constants and an orientation matrix for data collection were obtained by least-square refinement of the diffraction data for $[(PPh_2Me)_3Cu(I)]$. Diffraction data were collected in a series of ω scans in 1° oscillations and integrated using the Stoe X-AREA software package.[44] Numerical absorption correction was applied using the X-Red32 software. The structure was solved by direct methods and subsequent difference Fourier maps and then refined on F2 by a full-matrix least-squares procedure using anisotropic displacement parameters. All nonhydrogen atoms were refined with anisotropic displacement parameters. All refinements were performed using the X-STEP32, SHELXL-2014, and WinGX-2013.3 programs.[45–52] CIF was visualized using Olex-2-1.2. CCDC-2035215 for $[(PPh_2Me)_3Cu(I)]$ contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3 | RESULTS AND DISCUSSIONS

Deprotonation of 2-mercaptobenzothiazole or 2-mercapto-1-methylimidazole was carried out in ethanol by its reaction with potassium hydroxide. Then, equimolar amounts of copper iodide and an appropriate phosphine ligand was added consecutively, resulting, after work-up, in a yellow (mixtures **1**–**3**) and white powder (mixtures **4**–**6**), respectively, as shown in Scheme 1.

The catalytic activity of the so-prepared mixtures **1**–**6** was studied in A^3 coupling. The reaction of phenylacetylene (0.75 mmol), piperidine (0.75 mmol), and benzaldehyde (0.50 mmol) in water/THF (10:1) was chosen as a model reaction. Using 2.0 mg of Cu-containing mixture at rt, quantitative yields in propargylamine were obtained for all of precatalysts 1–3 (entries 1–3 of Table 1). Under the same conditions, but after 4 h of reactions, the propargylamine product was produced in 86% yield using **1** (entry 4, Table 1), and in 98% yield using **2** and **3** (entries 5–6, Table 1). Very good yields (73%–98%, entries 7–9, Table 1) were also obtained after 24 h using 2.0 mg of mixtures **1**–**3** but with quadrupled amount of reactants. A control experiment involving 2-mercaptobenzothiazole (entry 16, Table 1) in the absence of metal revealed crucial catalytic role of copper complexes in these coupling reactions.

Mixture **3** was then studied for the coupling reaction of structurally different aldehydes with amines and alkynes under optimized reaction condition (12-h



SCHEME 1 The procedure for the synthesis of copper complexes (mixture **1**–**6**) bearing thiolate and phosphine ligands

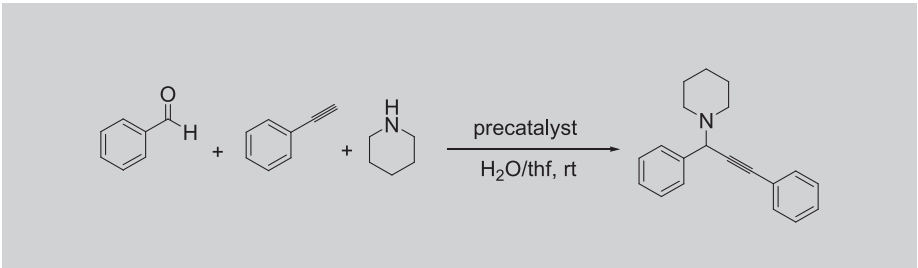


TABLE 1 Optimization of the reaction conditions for the reaction of benzaldehyde, piperidine, and phenylacetylene using mixtures **1**, **2**, and **3**[a]

Entry	Precatalyst	Temp (°C)	Time (h)	Yield (%)[b]
1	**1**	rt	12	>99
2	**2**	rt	"	>99
3	**3**	rt	"	>99
4	**1**	rt	4	86
5	**2**	rt	"	98
6	**3**	rt	"	98
7[c]	**1**	rt	12	83
8[c]	**2**	rt	"	73
9[c]	**3**	rt	"	98
10	$[(PPh_2Me)_3Cu(I)]$	rt	12	73
11	Orange residue	rt	12	56
12	**4**	rt	12	100
13	**5**	rt	12	75
14	**6**	rt	"	80
15	**10**	rt	12	98
16	2-Mercaptobenzothiazole	rt	12	<2

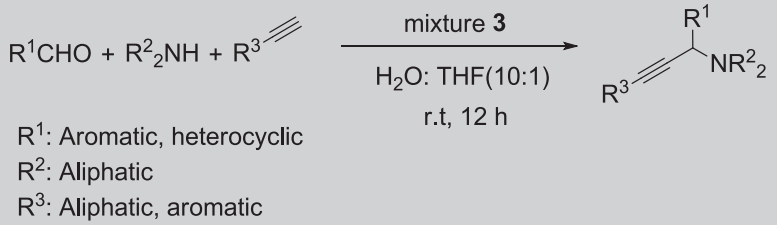
[a]Reaction conditions: benzaldehyde (0.50 mmol), piperidine (0.75 mmol), phenylacetylene (0.75 mmol), H_2O: THF (20:1, 2.0 ml), and 2.0 mg of precatalyst.
[b]Yields were determined by ^{1}HNMR.
[c]The amount of reactants was quadrupled compared with entries 1–6.

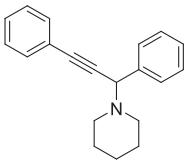
reaction time, 2.0-mg precatalyst and rt). Results, collected in Table 2, showed excellent yields for various aromatic aldehydes having electron-withdrawing groups (entries 2–5, Table 2) as well as for aldehydes containing electron-donating groups (entries 6–10, Table 2) in 12 h. It is worth mentioning that using mixture **3**, the reaction of heterocyclic and challenging aldehydes were carried out successfully, and the corresponding propargylamines were obtained in excellent yields (entries 11–14, Table 2). Reaction of 3-pyridinecarboxaldehyde with piperidine and pyrrolidine was also investigated and the yields were 98% and 97%, respectively (entries 11 and 12, Table 2). Furthermore, reactions of 3-thiophenecarbaldehyde with piperidine and 2-thiophenecarbaldehyde with morpholine gave 92% and 91% yields, respectively (entries 13 and 14, Table 2). In addition, reactions of biphenyl-4-carboxaldehyde with piperidine and phenylacetylene gave excellent yield in 24 h (entry 15, Table 2).

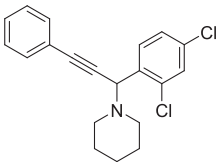
Reactions of heptanal as an aliphatic aldehyde with piperidine and phenylacetylene and also 1-octyne as an aliphatic alkyne with benzaldehyde and piperidine were studied affording desired products in 89% and 83% yields, respectively (entries 16 and 17, Table 2). Finally, reactions of diverse amines such as pyrrolidine, morpholine, and dimethylamine with benzaldehyde and phenylacetylene proceeded smoothly and the corresponding products were obtained in 97% yield (entries 18–20, Table 2). ^{1}H NMR and ^{13}C NMR spectra of all products listed in Table 2 (entries 1–20) are provided in the supporting information.

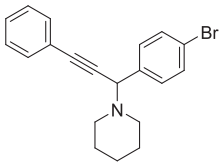
In order to gain insights into the active species operating in the in-situ process for catalytic A^3 coupling reactions from mixtures **1**–**3**, we carried out a crystallization in conditions similar to those of the catalytic runs. Thus, 20 mg of each mixture was gently warmed at 50°C–60°C in acetonitrile for 2 h and let to cool down to rt. Although only powder precipitated from mixtures **1** and **3**, in the case of mixture **2**, colorless crystals suitable for XRD analysis were obtained, along with a light orange solid (in the following: orange residue). The

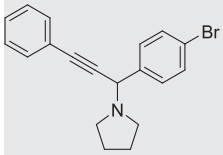
TABLE 2 Products from reactions of various aldehydes, amines, and alkynes obtained in the presence of mixture **3**[a]

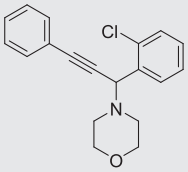


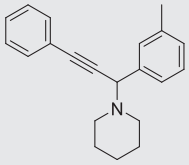

(entry 1) 97%

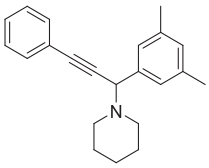

(entry 2) 93%

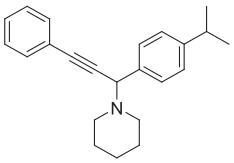

(entry 3) 89%

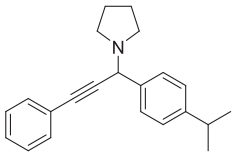

(entry 4) 91%

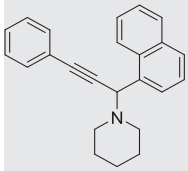

(entry 5) 90%

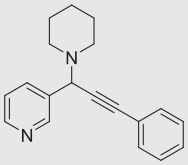

(entry 6) 94%

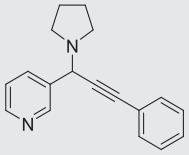

(entry 7) 91%

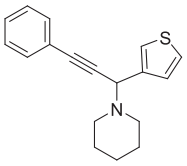

(entry 8) 90%

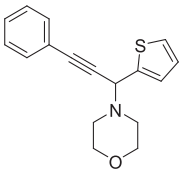

(entry 9) 93%

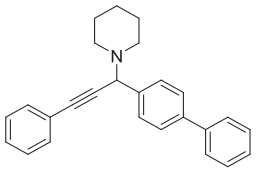

(entry 10) 88%

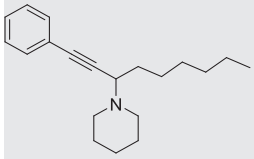

(entry 11) 98%

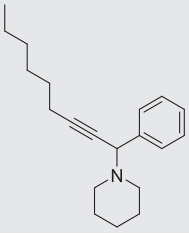

(entry 12) 97%

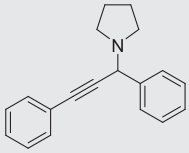

(entry 13) 92%

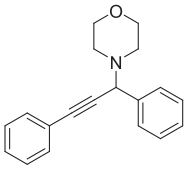

(entry 14) 91%

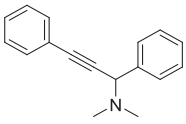

(entry 15)[b] 90%


(entry 16)[b] 89%


(entry 17)[b] 82%


(entry 18) 97%


(entry 19) 97%


(entry 20) 97%

[a]Reaction conditions: aldehyde (1 mmol), amine (1.5 mmol), alkyne (1.5 mmol), H_2O: THF (20:1, 2 ml), and precatalyst **3** (2 mg) at room temperature. Reaction time: 12 h. Isolated yields.
[b]Reaction time: 24 h.

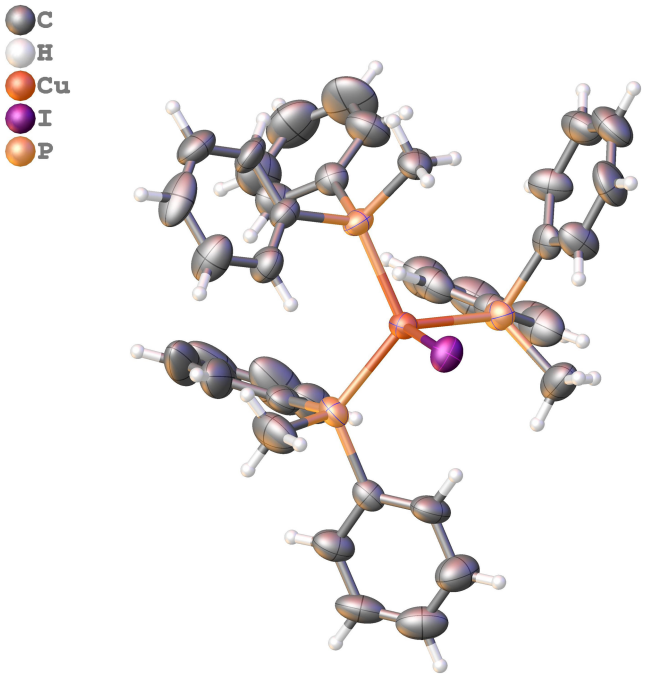


FIGURE 1 View of the molecular structure of $[(PPh_2Me)_3CuI]$

TABLE 3 Crystallographic data and structural refinement details for $[(PPh_2Me)_3CuI]$

Chemical formula	$C_{39}H_{39}CuIP_3$
M_r	791.06
Crystal system, space group	Orthorhombic, Pna21
Temperature (K)	298(2) K
a, b, c (Å)	20.258(4), 10.484(2) Å, c = 17.388 (4) Å
V (Å^3)	3,693.0(13) Å^3
Z	4
Radiation type	Mo $K\alpha$
Crystal size (mm)	0.300 × 0.300 × 0.200
Diffractometer	STOE IPDX II diffractometer
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0526, 0.1087, 0.959
No. of reflections	11,040
No. of parameters	400

molecular structure of the crystals obtained from **2** is shown in Figure 1 and reveals a monomeric tetrahedral $[(PPh_2Me)_3Cu(I)]$ complex in which the P–Cu–P and P–Cu–I angles lie close to the tetrahedral angle of 109.5°. To check whether $[(PPh_2Me)_3Cu(I)]$ or the orange residue were the active species in the mixture **2**, we carried out coupling reactions at rt for 12 h using 2.0 mg of $[(PPh_2Me)_3CuI]$ or 2.0 mg of the orange residue. In the case of $[(PPh_2Me)_3CuI]$, the yield dropped to 73% (entry 10, Table 1), whereas a 56% yield was achieved with the orange residue (entry 11, Table 1). This results seem to indicate that the thiolate heterocycle and a phosphine copper(I) complex synergically catalyze the A^3 reaction in our conditions (Table 3).

We decided therefore to submit mixtures **1**–**3** to HR ESI-MS analysis. The HRMS(+) analysis of **1**, **2**, and **3** in acetonitrile gave intense peaks due to $[Cu(PCy_3)(CH_3CN)]^+$, $[Cu(PPh_2Me)_2]^+$, and $[Cu(PPh_3)_2]^+$ ions, respectively, as shown in Figures 2–4.

Although signals for the expected heteroleptic copper complexes **7**, **8**, and **9**, in Figure 5,[53] were not present in the spectrograms, we propose that in mixtures **1**–**3** heteroleptic species similar to **7**–**9** (of general formula $[(PR_2R')_xCu_y(S^N)_z]$, with S^N deprotonated 2-mercaptobenzothiazole) can form and possibly be active as catalysts. If this hypothesis is correct, the ions detected by ESI-MS may be formed in the ionization chamber by loss of deprotonated 2-mercaptobenzothiazole. Due to mixed nature of metal complexes formed during the synthesis of **1**–**6**, a clear-cut NMR data could not be obtained; however, signals related to coordinated ligands in the mixtures were observed. ^{1}H NMR spectrum of **1** showed tricyclohexylphosphine and 2-mercaptobenzothiazole signals as multiplets at 2.21–0.86 ppm and 7.56–7.04 ppm, respectively (Figure S1). In the ^{1}H NMR spectrum of **3**, Figure S2, triphenylphosphine multiplets observed at 7.70–7.01 ppm. These data confirm abovementioned hypothesis that heteroleptic species **7**–**9** are formed in the synthesis of **1**–**3**, described in Scheme 1. A high intensity ^{13}C NMR spectrum for mixture **1** could not be obtained; however, sharp signals for coordinated triphenylphosphine ligand were observed in the ^{13}C spectrum of mixture **3**. In the ^{31}P NMR spectrum of **1** (Figure S8), two signals are observed perhaps related to $[Cu(PCy_3)(CH_3CN)]^+$, observed via ESI-MS, and heteroleptic **7**. Only one ^{31}P signal (Figure S9) was observed for mixture **3**.

FT-IR and UV data of **1** and **3** are provided in the supporting information. Both displayed characteristic sharp bands related to aliphatic and aromatic C–H stretching vibrations between 2,800 and 3,100 cm^{-1} as well as C═N and C═C stretching vibrations from 1,300 to 1,650 cm^{-1}. Distinct π–π^* transitions from 2-mercaptobenzothiazole aromatic ring were observed in the UV–Vis. spectra of **1** and **3** at 331 and 326 nm, respectively. An absorption band at 229 nm is indicative of coordinated triphenylphosphine ligand in mixture **3** (Figures S16 and S17).

As to the nature of the orange residue, it was found that it contained, together with other minor species, the homoleptic complex $Cu(\kappa^2\text{-}S,N)_2$ (S^N deprotonated 2-mercaptobenzothiazole) (**10** in Figure 5), as shown by comparison of the IR spectrum of the orange residue with

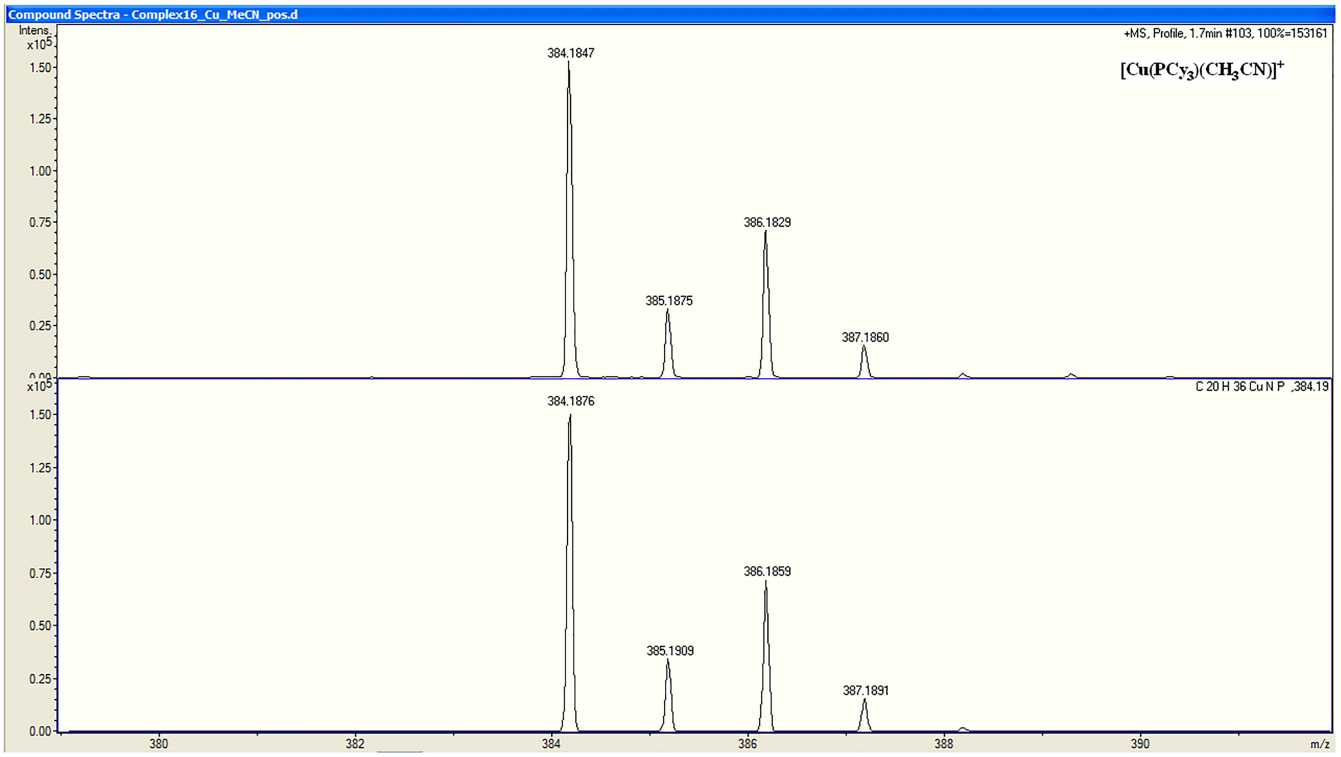


FIGURE 2 HRMS(+) spectrogram of **1** in acetonitrile showing the peak corresponding to $[Cu(PCy_3)(CH_3CN)]^+$. Top: experimental; bottom: calculated

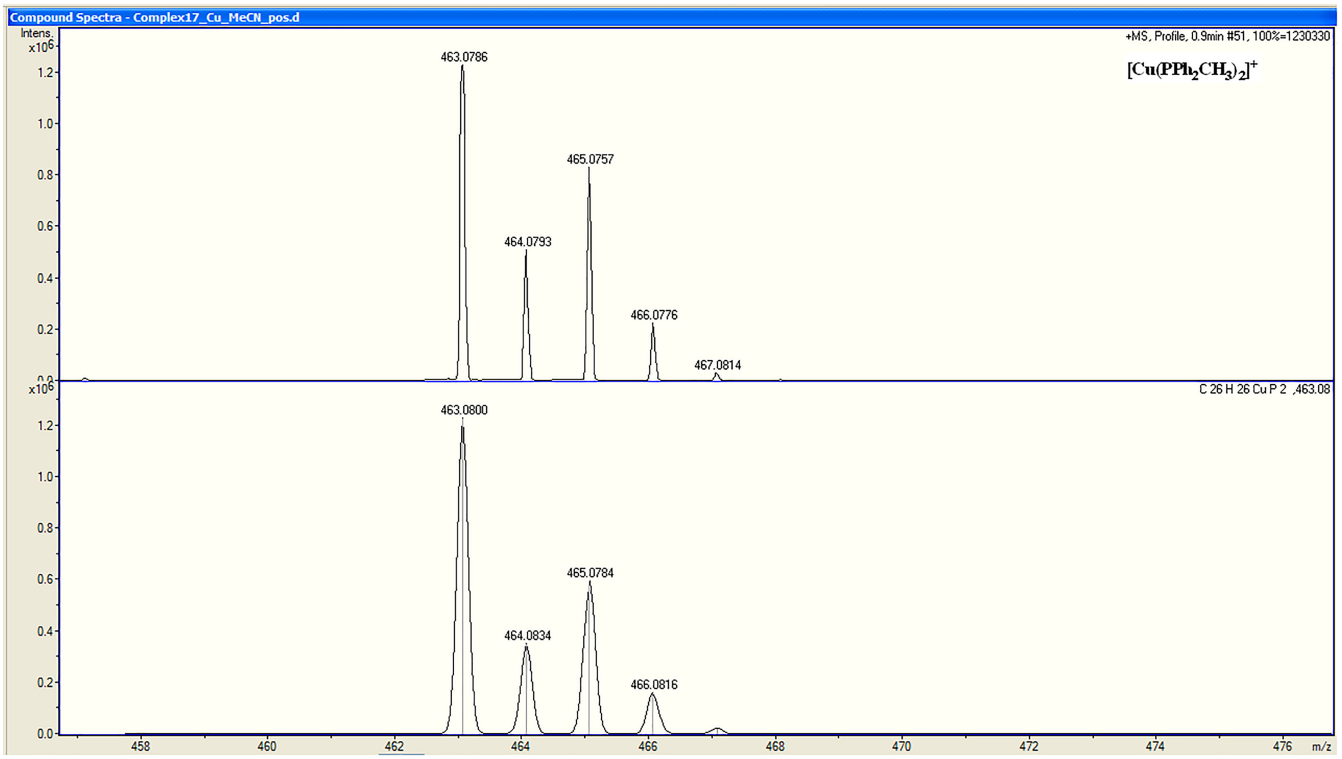


FIGURE 3 HRMS(+) spectrogram of **2** in acetonitrile showing the peak corresponding to $[Cu(PPh_2Me)_2]^+$. Top: experimental; bottom: calculated

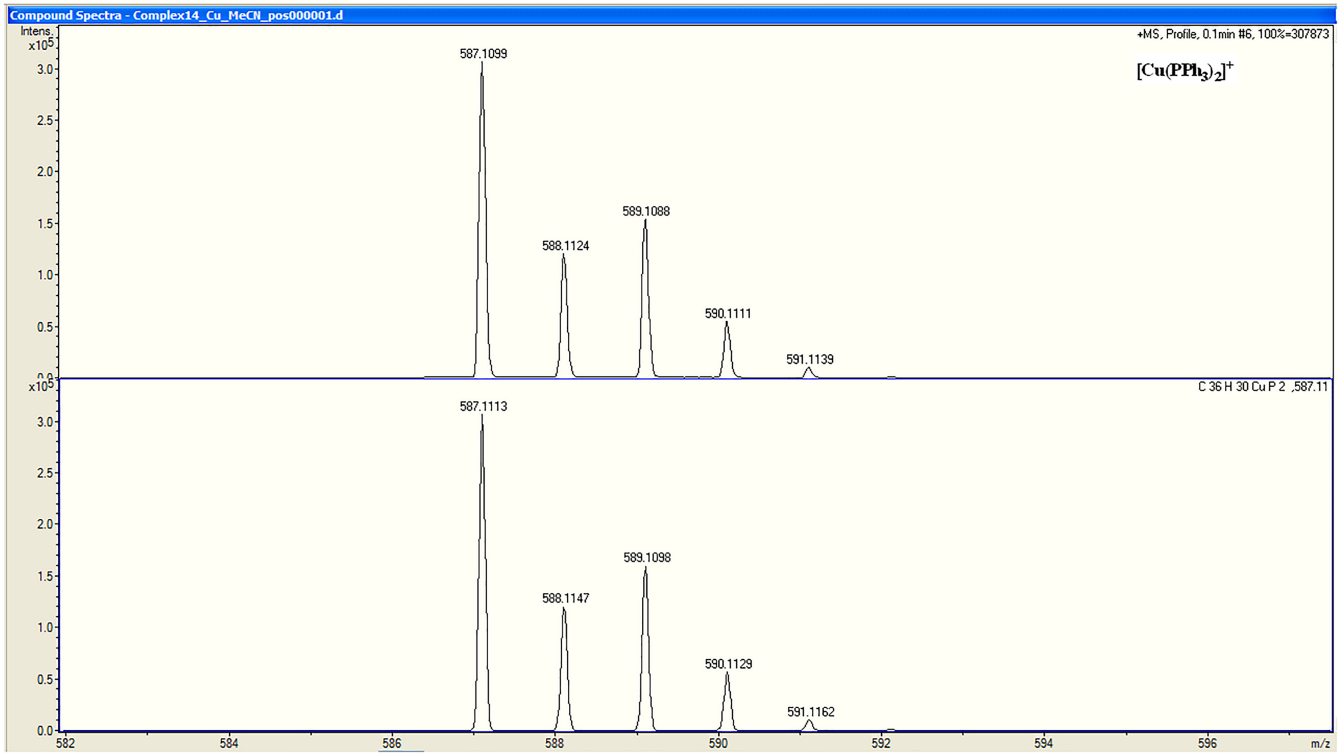


FIGURE 4 HRMS(+) spectrogram of **3** in acetonitrile showing the peak corresponding to $[Cu(PPh_3)_2]^+$. Top: experimental; bottom: calculated

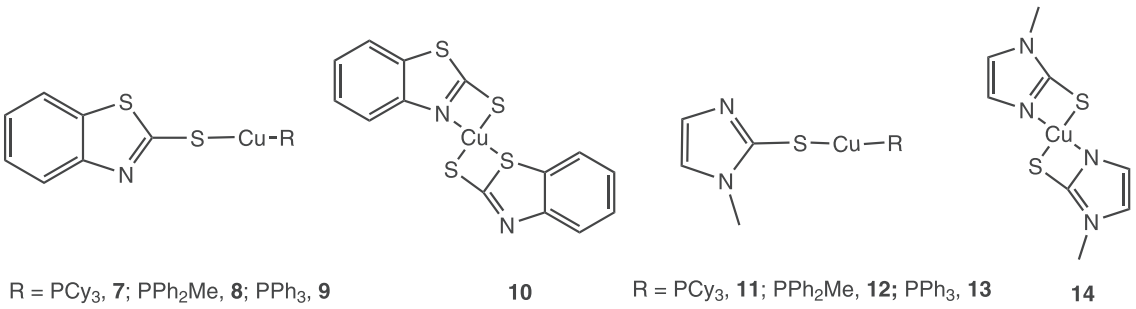


FIGURE 5 Proposed formulae of thiolate copper complexes. The presence of above copper complexes in **1**–**6** mixtures was shown by electrospray ionization mass spectrometry (ESI-MS) analysis

that of an authentic sample of **10** (Figure 6). The formation of **10** can occur by air oxidation of Cu(I) to Cu (II) and the fact that it was not detected by ESI-MS(+) analysis of **1**–**3** seems to indicate that it forms when mixtures **1**–**3** are heated in acetonitrile. Another possibility is that complex **10** can be present in mixtures **1**–**3,** but it is reluctant to be ionized in our experimental conditions (see below). To further confirm the structure of orange residue, its UV–Vis. spectra was compared with that of **10**, which shows almost complete overlap of their major peak at 330 and 326 nm (Figures S20 and S21).

The catalytic activity of pure **10** was checked in the A^3 model reaction, and it showed excellent activity at low catalyst loading (entry 15, Table 1), indicating **10** as one possible active species for the A^3 coupling.

As mentioned above, we prepared mixtures similar to **1**–**3** but with deprotonated methimazole in place of 2-mercaptobenzothiazole. Upon deprotonation, methimazole can adopt a monodentate coordination mode, binding through either sulfur or thioamido nitrogen atoms. A third mode in which a chelating κ^2-S,N coordination mode is adopted has also been reported.[54] The chemistry of this molecule with a multitude of transition metals ions, including copper, has been reported in the literature. Methimazole is a redox active molecule and treating copper (II) salts such as copper (II) nitrate in

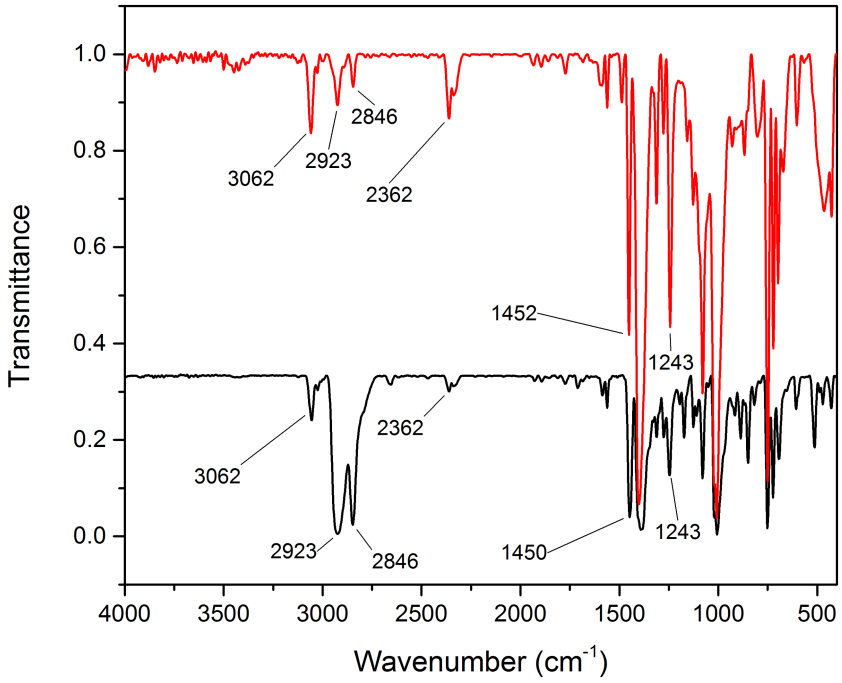


FIGURE 6 Fourier-transform infrared spectroscopy (FT-IR) spectra of **10** (homoleptic copper complex with thiolate ligands shown in Figure 5) (top) and orange residue (bottom), obtained by hot filtration of mixture **2** as described in the text

air results in the copper reduction and formation of methimazole disulfide and extrusion of one sulfur atom.[53]

The catalytic activity of mixtures **4**–**6** was investigated in the model A^3 coupling reaction. Although quantitative yield was obtained using mixture **4**, the reaction gave a 75% yield using mixture **5** and 80% yield using mixture **6**, under identical coupling reaction conditions.

The ESI-MS(+) analysis of the mixtures prepared with methimazole showed in all cases signals ascribable

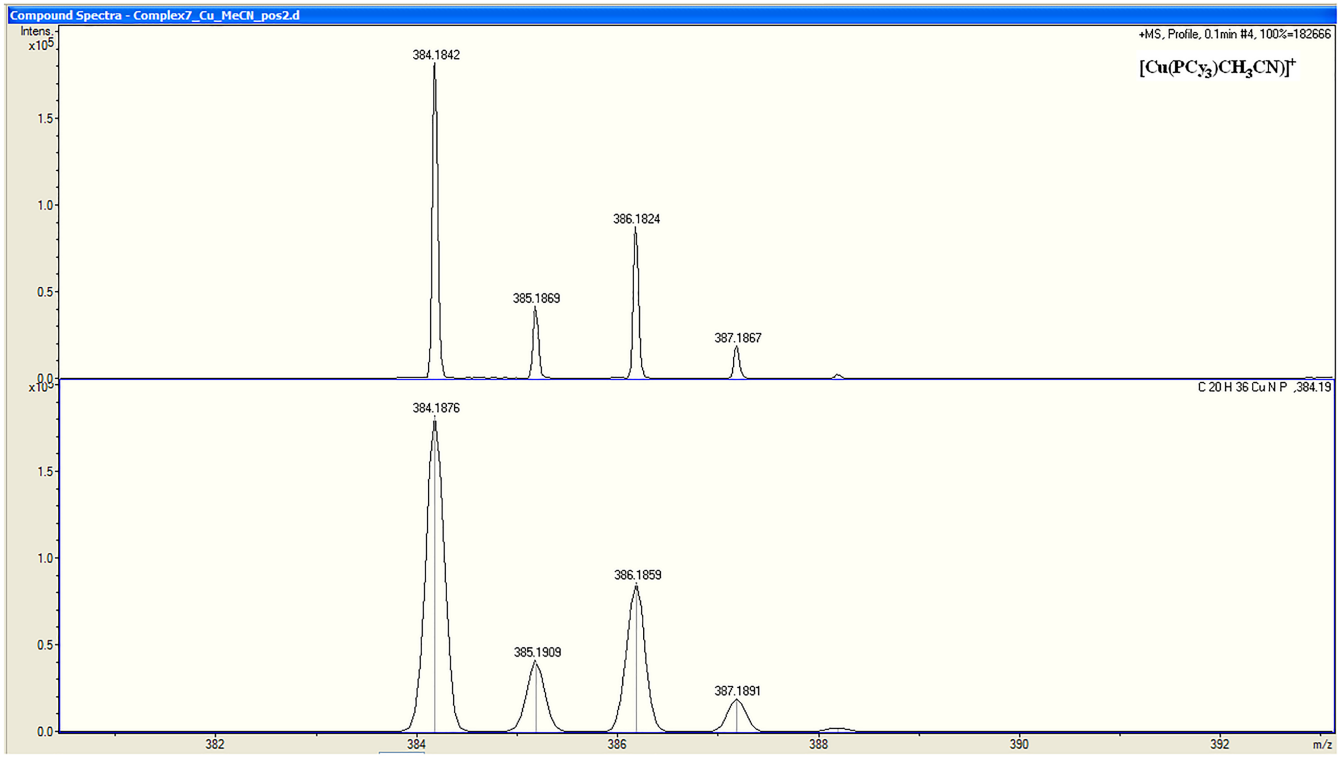


FIGURE 7 HRMS(+) spectrogram of **4** in acetonitrile showing the peak corresponding to $[Cu(PCy_3)(CH_3CN)]^+$. Top: experimental; bottom: calculated

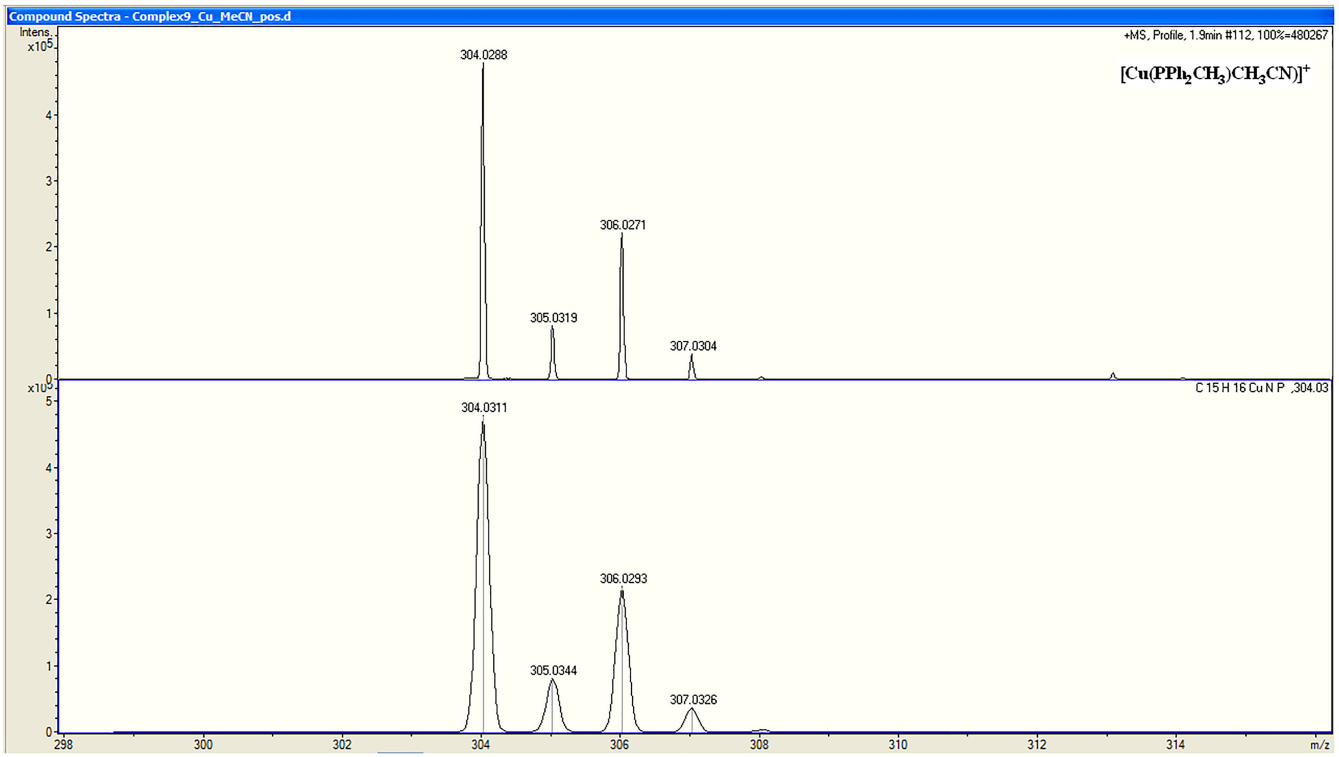


FIGURE 8 HRMS(+) spectrogram of **5** in acetonitrile showing the peak corresponding to $[Cu(PPh_2Me)(CH_3CN)]^+$. Top: experimental; bottom: calculated

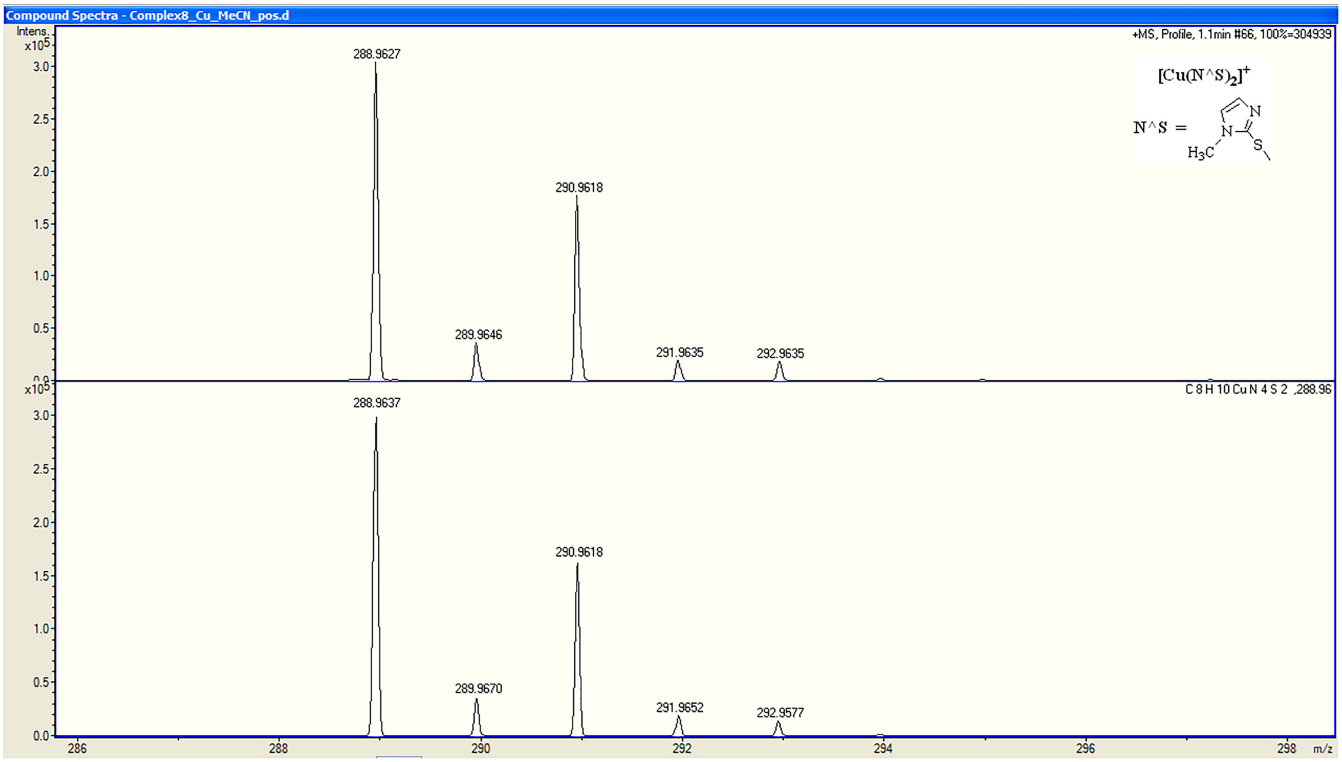


FIGURE 9 HRMS(+) spectrogram of **6** in acetonitrile showing the peak corresponding to $Cu(S^N)_2$ (S^N = deprotonated methimazole). Top: experimental; bottom: calculated

to copper complexes containing deprotonated methimazole (S^N) in the coordination sphere. In particular, mixture **4** gave intense signals due to $[Cu(PCy_3)(CH_3CN)]^+$ (Figure 7) plus less intense signal due to $\{[Cu(PCy_3)(S^N)] + H\}^+$ (found 457.1839 *m/z*; calculated 457.1868 Da); mixture **5** gave intense signals corresponding to $[Cu(PPh_2Me)(CH_3CN)]^+$ (Figure 8) plus less intense signals due to $\{[Cu(PPh_2Me)(S^N)] + H\}^+$ (found 377.0720 *m/z*; calculated 377.0303 Da); mixture **6** gave intense signals corresponding to $[Cu(S^N)_2]^+$ (Figure 9) plus less intense signals due to $[Cu(PPh_3)(CH_3CN)]^+$ (found 366.0450 *m/z*; calculated 366.0473 Da). It should be noted that the cation $[Cu(S^N)_2]^+$ presumably derives from monoelectron oxidation of one S^N anionic ligands from $[Cu(S^N)_2]$ (**14** in Figure 5), a process that seems not operative in the case of analogous species with deprotonated 2-mercaptobenzothiazole. ^{1}H NMR spectrum of **4** showed signals related to coordained tricyclohexylphosphine and methimazole as multiplets and a doublet at 1.89–1.26 and 6.66 ppm, respectively (Figure S3). A singlet for methyl is also observed at 3.57 ppm. In the ^{1}H NMR spectrum of **6**, triphenylphosphine multiplets were observed at 7.35–7.21 ppm, as shown in Figure S2. Methimazole resonance was observed as a doublet at 6.16 ppm. ^{13}C spectra of **4** and **6** were consistent with species observed in their ESI-MS spectrograms. Whereas tricyclohexylphosphine resonances in **4** were observed in 25–35 ppm region, only signals related to methimazole were observed for **6** at 125–135 ppm region, consistent with $[Cu(S^N)_2]^+$ signals observed in its ESI-MS analysis. Broad singlets observed at ^{31}P spectra of **4** and **6**, Figures S10 and S11, revealed coordinated phosphine ligands.

This results substantiate the formation of heteroleptic thiolate/phosphine Cu complexes during the preparation of mixtures **1**–**6** and validate the hypothesis that heterocyclic thiolate copper complexes are the active species in the A^3 coupling reaction. The detection of Cu species bearing the heterocyclic thiolate in mixtures with methimazole, but not with 2-mercaptobenzothiazole may be thus ascribed to different coordinating and redox properties of the two heterocyclic thiolates, with deprotonated methimazole more prone to be oxidized and less prone to dissociate from the metal, with respect to deprotonated 2-mercaptobenzothiazole.

4 | CONCLUSION

The mixtures obtained by mixing deprotonated 2-mercaptobenzothiazole or methimazole with CuI in the presence of a tertiary phosphine were active in the A^3 coupling of aldehyde, alkyne, and amine in water/THF 20:1 at rt. Very satisfactory results were obtained after 12 h reactions and the protocol, optimized for the mixture with triphenylphosphine and 2-mercaptobenzothiazole, was applied for the synthesis of 20 propargylamines with yields higher than 80%. ESI-MS(+) analyses on mixtures **1**–**6** revealed the presence of ions compatible with the formation of heteroleptic Cu complexes bearing the phosphine and the heterocyclic thiolate ligand, which are supposed to play a crucial role in catalysis.

ACKNOWLEDGMENTS

Funding from the Institute for Advanced Studies in Basic Sciences (IASBS) Research Council is acknowledged.

AUTHOR CONTRIBUTIONS

Abdollah Neshat: Conceptualization; data curation; formal analysis; project administration. **Mohammad Gholinejad:** Data curation; formal analysis; project administration. **Mahmoud Afrasi:** Data curation; formal analysis. **Piero Mastrorilli:** Data curation; formal analysis. **Stefano Todisco:** Data curation; formal analysis. **shirin gilanchi:** Formal analysis. **Farzane Osanlou:** Formal analysis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

ORCID

Abdollah Neshat https://orcid.org/0000-0002-1424-2292
Mahmoud Afrasi https://orcid.org/0000-0002-5492-3869
Piero Mastrorilli https://orcid.org/0000-0001-8841-458X
Stefano Todisco https://orcid.org/0000-0001-7863-3105
Shirin Gilanchi https://orcid.org/0000-0002-4281-7997
Farzane Osanlou https://orcid.org/0000-0001-6092-510X

REFERENCES

[1] a) J. J. Chen, D. M. Swope, K. Dashtipour, *Clin. Ther.* **2007**, *29*, 1825. b) M. Naoi, W. Maruyama, M. Shamoto-Nagai, H. Yi, Y. Akao, M. Tanaka, *Mol. Neurobiol.* **2005**, *31*, 81.
[2] a) I. E. Kopka, Z. A. Fataftah, M. W. Rathke, *J. Org. Chem.* **1980**, *45*, 4616. b) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407. c) V. V. Kouznetsov, L. Y. Vargas Méndez, *Synthesis* **2008**, *2008*, 491.
[3] V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790.
[4] M. Yu, Y. Wang, W. Sun, X. Yao, *Adv. Synth. Catal.* **2012**, *354*, 71.
[5] X. Yao, C.-J. Li, *Org. Lett.* **2005**, *7*, 4395.
[6] C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473.

[7] Z. Li, C. Wei, L. Chen, R. S. Varma, C.-J. Li, *Tetrahedron Lett.* **2004**, *45*, 2443.
[8] X. Chen, T. Chen, Y. Zhou, C.-T. Au, L.-B. Han, S.-F. Yin, *Org. Biomol. Chem.* **2014**, *12*, 247.
[9] A. Zhu, C. Du, Y. Zhang, L. Li, *J. Mol. Liq.* **2019**, *279*, 289.
[10] K. N. Sharma, A. K. Sharma, H. Joshi, A. K. Singh, *ChemistrySelect* **2016**, *1*, 3573.
[11] H. Veisi, L. Mohammadi, S. Hemmati, T. Tamoradi, P. Mohammadi, *ACS Omega* **2019**, *4*, 13991.
[12] J.-J. Chen, Z.-L. Gan, Q. Huang, X.-Y. Yi, *Inorg. Chim. Acta* **2017**, *466*, 93.
[13] M. Trivedi, G. Singh, A. Kumar, N. P. Rath, *Inorg. Chim. Acta* **2015**, *438*, 255.
[14] H. Veisi, N. Dadres, P. Mohammadi, S. Hemmati, *Mater. Sci. Eng., C* **2019**, *105*, 110031.
[15] P. Akbarzadeh, N. Koukabi, *Appl. Organomet. Chem.* **2020**, *34*, 1, e5395.
[16] R. Dodda, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 165.
[17] N. Esfandiary, F. Pazoki, A. Nakisa, K. Azizi, I. Radfar, A. Heydari, *Appl. Organomet. Chem.* **2020**, *34*, 1, e5725.
[18] Y. Liu, *ARKIVOC* **2014**, *1*, 1.
[19] C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, *2004*, 1472.
[20] C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268.
[21] M. Nasrollahzadeh, M. Sajjadi, F. Ghorbannezhad, S. M. Sajadi, *Chem. Rec.* **2018**, *18*, 1409.
[22] I. Jesin, G. C. Nandi, *Eur. J. Org. Chem.* **2019**, *2019*, 2704.
[23] D. Chandra, B. K. Jena, C. R. Raj, A. Bhaumik, *Chem. Mater.* **2007**, *19*, 6290.
[24] Y. Meng, D. Gu, F. Zhang, Y. Shi, L. Cheng, D. Feng, Z. Wu, Z. Chen, Y. Wan, A. Stein, D. Zhao, *Chem. Mater.* **2006**, *18*, 4447.
[25] N. Salam, S. K. Kundu, A. S. Roy, P. Mondal, S. Roy, A. Bhaumik, S. M. Islam, *Catal. Sci. Technol.* **2013**, *3*, 3303.
[26] N. Salam, S. K. Kundu, R. A. Molla, P. Mondal, A. Bhaumik, S. M. Islam, *RSC Adv.* **2014**, *4*, 47593.
[27] J. K. Cho, R. Najman, T. W. Dean, O. Ichihara, C. Muller, M. Bradley, *J. Am. Chem. Soc.* **2006**, *128*, 6276.
[28] A. Neshat, M. Afrasi, S. Gilanchi, M. Gholinejad, *ChemistrySelect* **2019**, *4*, 9268.
[29] M.-T. Chen, O. Navarro, *Synlett* **2013**, *24*, 1190.
[30] J. Cao, G. Xu, P. Li, M. Tao, W. Zhang, *ACS Sustainable Chem. Eng.* **2017**, *5*, 3438.
[31] M. Trose, M. Dell'Acqua, T. Pedrazzini, V. Pirovano, E. Gallo, E. Rossi, A. Caselli, G. Abbiati, *J. Org. Chem.* **2014**, *79*, 7311.
[32] M. Wang, P. Li, L. Wang, *Eur. J. Org. Chem.* **2008**, *2008*, 2255.
[33] J. D. Egbert, C. S. J. Cazin, S. P. Nolan, *Catal. Sci. Technol.* **2013**, *3*, 912.
[34] G. A. Price, A. K. Brisdon, S. Randall, E. Lewis, D. M. Whittaker, R. G. Pritchard, C. A. Muryn, K. R. Flower, P. Quayle, *J. Organomet. Chem.* **2017**, *846*, 251.
[35] A. Mariconda, M. Sirignano, C. Costabile, P. Longo, *Mol. Catal.* **2020**, *480*, 110570.
[36] G. Fang, X. Bi, *Chem. Soc. Rev.* **2015**, *44*, 8124.
[37] Y. He, M.-f. Lv, C. Cai, *Dalton Trans.* **2012**, *41*, 12428.
[38] a) P. Yadav, M. Yadav, R. Gaur, R. Gupta, G. Arora, P. Rana, A. Srivastava, R. K. Sharma, *ChemCatChem* **2020**, *12*, 2488. b) M. Milen, G. Györke, A. Dancsó, B. Volk, *Tetrahedron Lett.* **2020**, *61*, 151544. c) S. Yan, S. Pan, T. Osako, Y. Uozumi, *ACS Sustainable Chem. Eng.* **2019**, *7*, 9097. d) J. C. S. Terra, A. Moores, F. C. C. Moura, *ACS Sustainable Chem. Eng.* **2019**, *7*, 8696. e) A. Shaabani, M. Shadi, R. Mohammadian, S. Javanbakht, M. T. Nazeri, F. Bahri, *Appl. Organomet. Chem.* **2019**, *33*, e5074. f) P. Kaur, B. Kumar, V. Kumar, R. Kumar, *Tetrahedron Lett.* **2018**, *59*, 1986. g) R. Bonyasi, M. Gholinejad, F. Saadati, C. Nájera, *New J. Chem.* **2018**, *42*, 3078. h) M. Gholinejad, F. Saadati, S. Shaybanizadeh, B. Pullithadathil, *RSC Adv.* **2016**, *6*, 4983.
[39] Q.-M. Qiu, M. Liu, Z.-F. Li, Q.-H. Jin, X. Huang, Z.-W. Zhang, C.-L. Zhang, Q.-X. Meng, *J. Mol. Struct.* **2014**, *1062*, 125.
[40] I. P. Khullar, U. Agarwala, *Can. J. Chem.* **1975**, *53*, 1165.
[41] L. Yuan, W.-y. Ma, C. Wang, W.-x. Zhou, J. Niu, J. Li, *Transition Met. Chem.* **2014**, *39*, 859.
[42] H. A. El-Asmy, I. S. Butler, Z. S. Mouhri, B. J. Jean-Claude, M. Emmam, S. I. Mostafa, *Inorg. Chim. Acta* **2016**, *441*, 20.
[43] P. J. Cox, P. Aslanidis, P. Karagiannidis, S. K. Hadjikakou, *Polyhedron* **1999**, *18*, 1501.
[44] C. Stoe, X–AREA: program for the acquisition and analysis of data, version 1.30, Stoe & Cie GmbH: Darmatadt, Germany, **2005**.
[45] F. H. Allen, O. Johnson, G. P. Shields, B. R. Smith, M. Towler, *J. Appl. Crystallogr.* **2004**, *37*, 335.
[46] L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837.
[47] C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler, J. van der Streek, *J. Appl. Crystallogr.* **2006**, *39*, 453.
[48] M. N. Burnett, C. K. Johnson, *ORTEP-III Report ORNL-6895*, Oak Ridge National Laboratory, Tennessee, USA **1996**.
[49] A. L. Spek, *J. Appl. Crystallogr.* **2003**, *36*, 7.
[50] G. M. Sheldrick, *Acta Crystallogr, Sect. A: Found. Crystallogr.* **2008**, *64*, 112.
[51] P. Coppens, L. Leiserowitz, D. Rabinovich, *Acta Crystallogr.* **1965**, *18*, 1035.
[52] C. Stoe, X-STEP32: crystallographic package, version 1.07b, Stoe & Cie GmbH, Darmstadt, Germany, **2000**.
[53] L. Bin, Q. Qi-Ming, Y. Yue, J. Yu-Han, J. Qiong-Hua, Z. Cun-Lin, *Zeitschrift für Kristallographie - New Crystal Structures* **2013**, *228*, 287.
[54] F. Isaia, M. C. Aragoni, M. Arca, A. Bettoschi, C. Caltagirone, C. Castellano, F. Demartin, V. Lippolis, T. Pivetta, E. Valletta, *Dalton Trans.* **2015**, *44*, 9805.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Neshat A, Gholinejad M, Afrasi M, et al. Heterocyclic thiolates and phosphine ligands in copper-catalyzed synthesis of propargylamines in water. *Appl Organomet Chem*. 2021;35:e6180. https://doi.org/10.1002/aoc.6180