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$[Cu_8(\mu_4\text{-}H)\{S_2P(OEt)_2\}_6](PF_6)$: A Novel Catalytic Hydride-Centered Copper Cluster for Azide-Alkyne Cycloaddtion

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Abstract A hydride-centered dithiophosphate cluster $[Cu_8(\mu_4\text{-}H)\{S_2P(OEt)_2\}_6](PF_6)$ (**1**)] previously developed by us was applied as a new catalyst to the 1,3-dipolar cycloaddition of organic azides and alkynes for preparing substituted trizoles. With the required catalyst loading as low as 0.4 mol%, the reactions of terminal alkynes with BnN_3 all proceeded smoothly at ambient temperature in CH_3CN to exclusively produce 1,4-triazoles in good yields. For these reactions, it is assumed that the formation of the requisite copper acetylide intermediate is facilitated by the abstraction of the terminal hydrogen of alkynes by the hydride released from the central of the cluster. With only few examples being documented in literatures, the reactions of a range of internal alkynes have also been realized under the catalysis of **1** (0.8 mol%) in DMF at elevated temperature, to yield 1,4,5-trisubstituted triazoles in moderate to high yields. Our study has provided a preliminary insight into the effect of sulfur-based ligands on the activity of copper ion.

Keywords Copper(I) cluster · 1,3-Dipolar cycloaddition · Alkynes · Triazoles · Click chemistry

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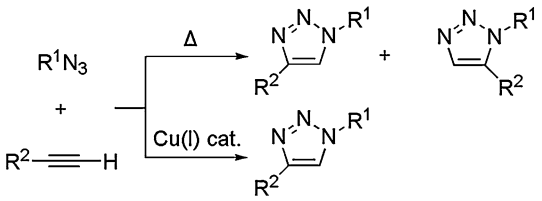
1 Introduction

The copper(I)-catalyzed 1,3-dipolar cycloaddition of organic azides with alkynes (CuAAC) has emerged as an extremely powerful method for preparing substituted triazoles [1–3], which has found wide applications in numerous fields [4–15] such as drug discovery [4–6], biomodifications [7–10], material chemistry [4, 11–14] and surface science [15]. As compared with the thermal cycloaddition of terminal alkynes (Huisgen reaction) usually producing an isomeric mixture [16], the copper(I) catalysis leads to a major improvement in both regioselectivity and rate to exclusively produce 1,4-triazoles (vs 1,5-regioisomers) under relatively mild conditions (Scheme 1), to thus fulfill the requirement of "click chemistry". The previous works have demonstrated that some commercially available copper(I) salts such as CuBr [17] and CuI [18] or even metallic copper [19] can be used to catalyze the reaction. Nevertheless, the innovation of more efficient and/or robust catalytic systems has always attracted considerable interests. Among the developed methods, the most widely employed ones are those involving the in situ generation of catalytically active Cu(I) from Cu(II) salts, such as the combination of $CuSO_4$/Na-ascorbate [19, 20] and $CuSO_4$/Cu [5]. Besides, the applications of copper nanoparticles [21] or the π-donating ligand-coordinated copper(I) species [22] to CuAAC have also been well documented in literatures, as exemplified by the recent advance in using *N*-heterocyclic carbene (NHC)-stabilized copper complexes to catalyze the reaction [23–25].

Our research group previously reported [26] a novel hydride-centered Cu_8(I)-dithiophosphate (dtp) cluster formulated as $[Cu_8(\mu_4\text{-}H)\{S_2P(OEt)_2\}_6](PF_6)$ (**1**) (Scheme 2), which was readily prepared by mixing tetrakis(acetonitrile)



Scheme 1 1,3-Dipolar cycloaddition of terminal alkynes with azides

copper(I) hexafluorophosphate, diethyl dithiophosphate ammonia salt and sodium borohydride together in a ratio of 8:6:1. The X-ray analysis revealed that **1** possessed an interesting and rare coordination pattern, in which, the hydride-centered tetracapped tetrahedral Cu_8 core is surrounded by an icosahedral sulfur cage composed of 12 S atoms out of six dtp ligands. Furthermore, we observed that cluster **1** exhibited high solubility in various organic solvents (e.g. CH_3CN, DMF, CH_2Cl_2, THF, etc.) and good air-stability, which appeared to be suited for catalysis. A literature search disclosed that the application of such sulfur ligand-based complexes to the 1,3-dipolar cycloaddition was very rare [27]. We therefore decided to attempt **1** to the reaction for exploring its catalytic activity. Herein we wish to report our preliminary results.

2 Experimental

2.1 Materials and Methods

All reagents were purchased from commercial suppliers and used without further purification. All reactions were performed under an atmosphere of nitrogen except otherwise noted. Tetrahydrofuran was freshly distilled from sodium-benzophenone, and dichloromethane was freshly distilled from CaH_2, acetonitrile, hexane and acetone were distilled from molecular sieves (4 Å) before use. TLC analysis was carried out on glass-backed silica gel plates, and visualized by UV light. The products were purified by flash chromatography using silica gel (70–230 mesh). ^1H, ^{13}C NMR spectra were recorded on 400 MHz spectrometers using deuteriochloroform ($CDCl_3$) as solvent. Chemical shifts measurements are reported in delta (δ) units. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants (*J*) are reported in Hertz (Hz). The resonances of infrared (IR) spectra are reported in wave numbers (cm^{-1}). High resolution mass spectra (HRMS) were determined in fast atom bombardment (FAB) or electron impact (EI) modes. Cluster **1** was prepared following our previously reported procedure [26] and stored at 0 °C before each use. The unknown products from this study (**2c**, **2i**, **3c**, **3d**, **3f**, **3h/3h′** and **3j/3j′**) were all characterized by spectroscopic methods as well as the X-ray analysis (**2i**, **3f** and **3j**, CCDC 831728-831730).

2.2 Synthesis of 1

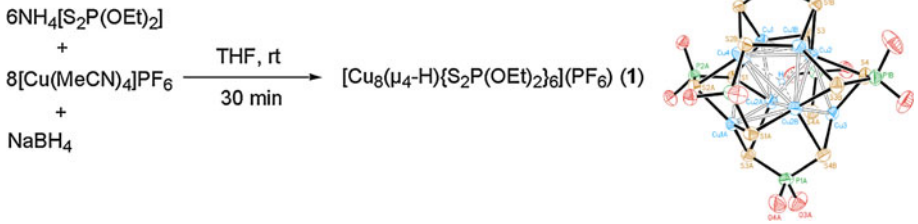
See ref. [26]

2.3 Typical Experimental Procedure for Cycloaddition of Terminal Alkynes (2a)

To a stirred solution of **1** (8 mg, 0.4 mol%, 1.6 M) in acetonitrile (2.5 mL), phenylacetylene (0.102 g, 1 mmol) and benzyl azide (0.133 g, 1 mmol) were successively added under N_2. The mixture was stirred at room temperature for 4 h then filtrated through a Celite pad, washed with ethyl acetate (10 mL) and concentrated. The residue was purified by flash chromatography on silica gel (hexane–ethyl acetate = 8:1) to afford **2a** (214 mg, 91 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.81 (m, 2H), 7.41–7.29 (m, 9H), 5.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 130.6, 129.1, 128.9, 128.8, 128.2, 128.1, 125.7, 54.3.

2.4 Typical Procedure for Cycloaddition of Internal Alkynes (3a)

To a stirred solution of **1** (16 mg, 0.8 mol%, 1.6 M) in DMF (5 mL) under N_2, diethylcarboxylate acetylene (0.170 g, 1 mmol) and benzyl azide (0.133 g, 1 mmol) were successively added. The mixture was then heated at 120 °C for 12 h and cooled to rt. After concentration under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane–ethyl acetate = 10:1,



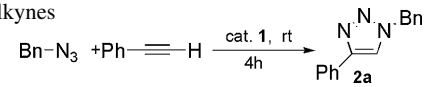
Scheme 2 Preparation and thermal ellipsoid plot of **1** (with ethyl groups omitted for clarity)

5:1) to afford **3a** (273 mg, 90 %) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.29 (m, 3H), 7.23–7.21 (m, 2H), 5.77 (s, 2H), 4.40 (q, J = 7.2 Hz, 2H), 4.28 (q, J = 7.3 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.8, 140.4, 134.0, 129.9, 128.9, 128.7, 128.0, 62.8, 61.8, 53.7, 14.1, 13.8.

3 Results and Discussion

Our initial investigation was directed to the cycloaddition of terminal alkynes. By using 0.4 mol% of **1**, we first screened several solvents including hexane, dichloromethane, acetone, tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF) and acetonitrile by the reaction between phenylacetylene and benzyl azide (BnN_3) (Table 1, entries 1–6). At room temperature, all reactions completed in 4 h to afford 1-benzyl-4-phenyl-1,2,3-triazole (**2a**) as the sole regioisomer in 52–91 % yields, and the best conversion was obtained in acetonitrile (entry 6). On this basis, we subsequently carried out the reactions respectively in 0.8, 0.3 and 0.2 mol% catalytic loadings. As shown in entries 7–9, the use of 0.8 mol% of **1** did not improve the yield (entry 7) as compared with the yield in entry 6, while both reduced loadings gave the poorer conversions (entries 8 and 9). Therefore the conditions in entry 6 (0.4 mol% of **1**/acetonitrile/rt) were considered to be our optimal choice.

Table 1 Optimization of reaction conditions for cycloaddition of terminal alkynes

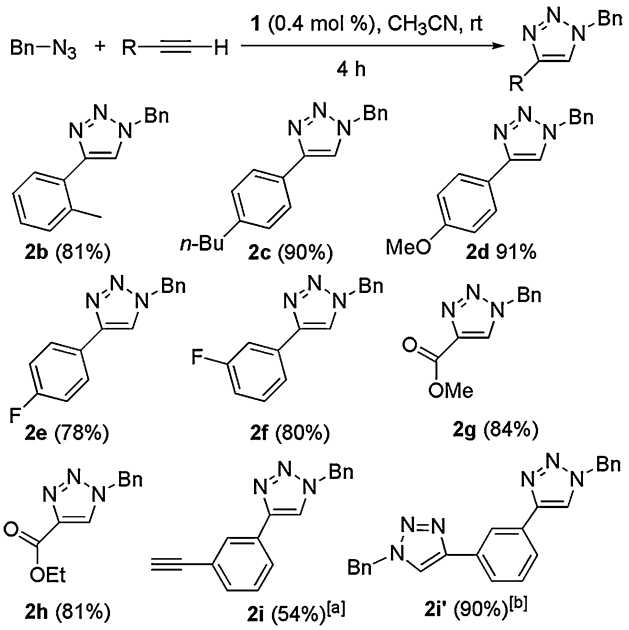


Entry[a,b]	Catalytic conditions	Yield (%)[c]
1	0.4 mol% of **1**/hexane	59
2	0.4 mol% of **1**/CH_2Cl_2	52
3	0.4 mol% of **1**/acetone	71
4	0.4 mol% of **1**/THF	82
5	0.4 mol% of **1**/DMF	60
6	0.4 mol% of **1**/CH_3CN	91
7	0.8 mol% of **1**/CH_3CN	90
8	0.3 mol% of **1**/CH_3CN	77
9	0.2 mol% of **1**/CH_3CN	58
10	None of **1**/CH_3CN	–

[a] All reactions were performed under a N_2 atmosphere. For a given catalytic system, it was observed that the reactions carried out under a N_2 atmosphere often resulted in better and more consistent yields of **2a** than the reactions without the N_2 protection, e.g. 71–84 % yields for the reactions under the catalytic system of 0.4 mol % of 1/CH_3CN/rt (Table 1, entry 6) without the N_2 protection

[b] All reactions were performed by using 1.6 M of **1** and 1 equiv of BnN_3

[c] Isolated yield



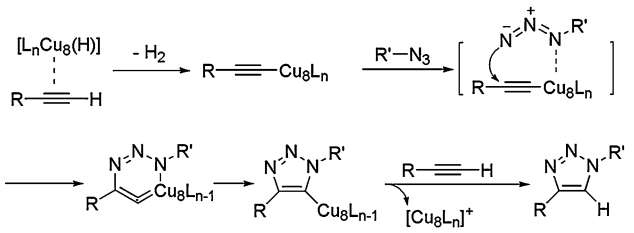
Scheme 3 Copper cluster-catalyzed 1,3-dipolar cycloaddition of terminal alkynes [*a*] 1.0 equiv of BnN_3 was used. [*b*] 3.0 equiv of BnN_3 were used

To verify the role of **1**, we also carried out a blank reaction without the catalyst and found that no cycloaddition could take place even after prolonged time (>48 h) (entry 10).

Under the optimized conditions, we continued to conduct the reactions of a range of selected terminal alkynes with BnN_3 (1 equiv), and found that all reactions proceeded efficiently to give triazoles **2b–h** in good to excellent isolated yields (78–91 %) (Scheme 3). For the reaction of 1,3-diethynylbenzene, the use of 1 equiv of BnN_3 led to the formation of mixed mono-triazole **2i** and bis-triazole **2i′** in 54 and 15 % isolated yield, respectively. When 3 equiv of BnN_3 was employed, the full consumption of the triple bonds was achieved in giving **2i′** as the sole product (isolated: 90 %).

To rationalize the catalytic mechanism, we independently treated phenylacetylene and BnN_3 with 1 equiv of **1** in acetonitrile. After stirring for 4 h at room temperature, the TLC analysis indicated no change of BnN_3, whereas the disappearance of phenylacetylene along with the formation of a high polar complex. Therefore, it is speculated that the catalytic process should begin with the formation of the copper(I) acetylide intermediate as generally accepted for the reaction of terminal alkynes (Scheme 4) [19, 28–30]. Regarding the hydride-donating capability of **1**[1], we herein

[1] The hydride-donating ability of **1** has recently been realized by its ability to reduce 2-cyclohexenone into cyclohexanone. Treatment of 2-cyclohexenone (10 mg, 0.104 mmol) with **1** (624 mg) in THF (25 mL) at ambient temperature for 12 h resulted in 30 % conversion into cyclohexanone as monitored by gas chromatography



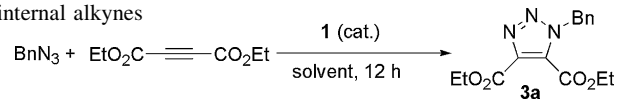
Scheme 4 Proposed mechanism for **1**-catalyzed cycloaddition of terminal alkynes

assume that the initial acetylide-formation in our case can be particularly facilitated with the abstraction of the terminal hydrogen by the hydride released from the central of the cluster. The resulting acetylide intermediate then engages in an addition with azide to afford a six-membered metallacycle. The ring contraction of which produces a copper-metallated triazole, which subsequently undergoes the hydrogen-exchange with another alkyne to give the triazole product. The released catalyst then participates in another cycle of cycloaddition.

After completing the aforementioned works, we then turned our attention to investigating the copper-catalyzed 1,3-dipolar cycloaddition of internal alkynes. So far, there are only few examples on this type of reactions being documented in literatures [23, 24]. Although the same goal can nowadays be attended by ruthenium- or zinc-catalysis [31, 32], yet the copper-based catalysts should be of more use in practice in term of relatively low cost.

At first, the optimal conditions for terminal alkynes (0.4 mol% of **1**/acetonitrile) were attempted to the reaction between BnN_3 and diethyl acetylenedicarboxylate. After proceeding for 12 h at room temperature, the reaction produced triazole **3a** in 61 % yield (Table 2, entry 1). A better conversion could be obtained in acetonitrile when the catalytic loading was increased to 0.8 mol% (entry 2, 77 %). In 0.8 mol% loading, we further tested several solvents including hexane, dichloromethane, THF, water and DMF (entries 3–7), and received the best yield from DMF (entry 7, 80 %). In DMF, it was also observed that the increment on the catalytic amount to 1 mol% did not improve the yield (entry 8, 76 %) while the reduction to 0.4 mol% gave the poorer conversion (entry 9, 69 %). Notably, no cycloaddition could be detected in DMF at room temperature in the absence of **1** (entry 10), thus validating the essential role that **1** played on the cycloaddition. To further improve the yield, we then carried out the reaction at 120 °C in DMF, and found that **3a** could be formed in an excellent yield under such conditions (entry 11, 90 %). A blank reaction at the same temperature still could produce **3a** but in much poorer yield (entry 12, 57 %) to therefore confirm the effect of the cluster on the cycloaddition.

Table 2 Optimization of reaction conditions for cycloaddition of internal alkynes



Entry[a]	Catalytic conditions	Yield (%)[b]
1	0.4 mol% of **1**/CH_3CN/rt	61
2	0.8 mol% of **1**/CH_3CN/rt	77
3	0.8 mol% of **1**/hexane/rt	64
4	0.8 mol% of **1**/CH_2Cl_2/rt	48
5	0.8 mol% of **1**/THF/rt	56
6	0.8 mol% of **1**/H_2O/rt	68
7	0.8 mol% of **1**/DMF/rt	80
8	1 mol% of **1**/DMF/rt	76
9	0.4 mol% of **1**/DMF/rt	69
10	None of **1**/DMF/rt	–
11	0.8 mol% of **1**/DMF/120 °C	90
12	None of **1**/DMF/120 °C	57

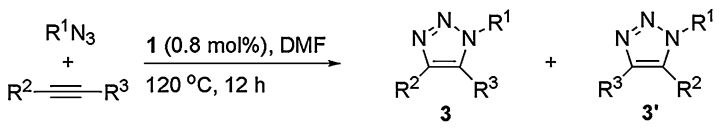
[a] All reactions were performed with 1.6 M of **1** and 1 equiv of BnN_3

[b] Isolated yield

The application of the conditions in entry 11 of Table 2 to the reactions between benzyl, 1-adamantyl and 4-methoxybenzyloxycarbonyl azides and a variety of internal alkynes led to the formation of triazoles **3b–3m/m′** in moderate to excellent yields (45–98 %) after isolation (Scheme 5). As can be seen, the reactions proceeded efficiently not only for the alkynes bearing the electron-withdrawing carboxylate groups but also for the alkynes with the alkyl and/or phenyl substituents known to be less reactive for the 1,3-dipolar cycloaddition. Among which, the yields of the reactions with BnN_3 were uniformly higher than those of the corresponding reactions with 1-adamantyl and 4-methoxybenzylcarbonyl azides (e.g. **3a** vs **3c** and **3d**), which could possibly be attributed to the less favorable steric and/or electronic natures of the azides. In addition, the formation of the mixtures of two regioisomers (**3g/3g′→3m/3m′**) was observed for all unsymmetrically substituted alkynes.

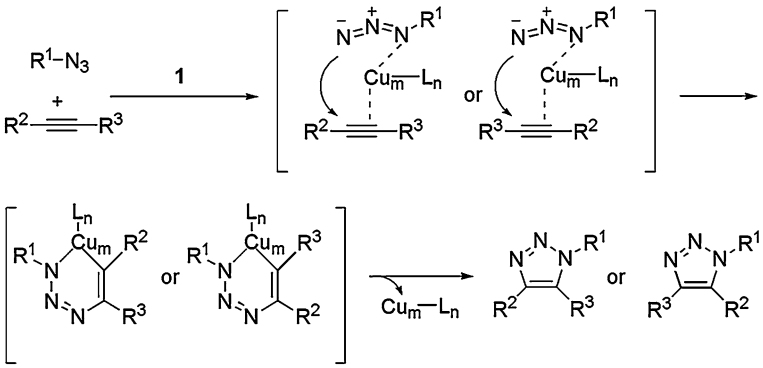
Unlike observed for terminal alkynes, we found that none of the employed internal alkynes could form detectable complex with **1** (1 equiv) alone in DMF. However, after the azides were introduced to the reaction mixtures, the gradual formation of the triazole products becomes noticeable as monitored by TLC analysis. It is therefore proposed that the cycloaddition can only be induced after the cluster **1** simultaneously coordinates with both components to give the formation of a six-membered metallacyclic intermediate [22]. From which, the triazole product(s) is generated accompanied by the release of the cluster for the next catalytic cycle (Scheme 6). This proposal agrees with the formation of the isomeric mixtures

Scheme 5 Copper cluster-catalyzed 1,3-Dipolar cycloaddition of internal alkynes [*a*] Isolated yield. [*b*] Ratio was determined by integration of 400 MHz NMR spectrum



product(s)	yield (%)[a]	ratio (3/3')[b]
3b (R1 = Bn, $R^2 = R^3 = CO_2Me$)	82	
3c (R^1 =1-adamantyl, $R^2 = R^3 = CO_2Et$)	81	
3d (R^1 = 4-methoxybenzylcarbonyl, $R^2 = R^3 = CO_2Et$)	45	
3e (R^1 = Bn, $R^2 = R^3$ = Ph)	68	
3f (R^1 = Bn, $R^2 = R^3$ = 4-methoxyphenyl)	56	
3g and **3g'** (R^1 = Bn, $R^2 = CO_2Et$, R^3 = Ph)	98	63/73
3h and **3h'** (R^1 = 1-adamantyl, $R^2 = CO_2Et$, R^3 = Ph)	48	52/48
3i and **3i'** (R^1 = Bn, $R_2 = CO_2Et$, R_3 = Me)	99	72/28
3j and **3j'** (R^1 = 1-adamantyl, $R_2 = CO_2Et$, R_3 = Me)	85	55/45
3k and **3k'** (R^1 = Bn, R^2 = Ph, R^3 = 4-methoxyphenyl)	51	50/50
3l and **3l'** (R^1 = Bn, R^2 = Ph, R^3 = Me)	48	52/48
3m and **3m'** (R1 = Bn, R^2 = Ph, R^3 = Bu)	50	47/53

Scheme 6 Proposed mechanism for **1**-catalyzed cycloaddition of internal alkynes



for the unsymmetrically substituted alkynes since the initial addition step should not have a strong regioselective bias.

4 Conclusion

In summary, the cluster **1** has been successfully applied as a new and efficient catalyst to the 1,3-dipolar cycloaddition for both terminal and internal alkynes. As compared with those previously developed nitrogen- or phosphorus-based ligands, our study has demonstrated that sulfur ligands may have the comparable or even higher capability in enhancing the activity of copper(I) ion, and consequently open a new perspective for the development of novel catalytic systems. At current stage, the exact role(s) that the sulfur ligand within the cluster played on the catalysis is still not clear for us. An investigation to solve this puzzle is ongoing in our group.

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