Chinese Journal of Catalysis 37 (2016) 1446–1450

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Communication

Highly active binuclear Cu(II) catalyst bearing an unsymmetrical bipyridine-pyrazole-amine ligand for the azide-alkyne cycloaddition reaction

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A R T I C L E I N F O

Article history:
Received 12 March 2016
Accepted 18 April 2016
Published 5 September 2016

Keywords:
N-heterocycle ligand
Cu complex
1,3-Dipolar cycloaddition
Alkynes
Azides

A B S T R A C T

Ligands containing NH groups often show special characteristics. In this paper, a well-defined dinuclear Cu(II) complex bearing an unsymmetrical bipyridine-pyrazole-amine ligand was synthesized by the condensation of N–H to release H_2O. Using sodium L-ascorbate as a reductant, the binuclear complex showed excellent activity in 1,3-dipolar cycloaddition reactions between alkynes and azides to obtain 1,4-disubstituted triazoles in 95%–99% isolated yields.

The Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction between alkynes and azides (CuAAC) for constructing triazole cycles, which was independently reported by Sharpless et al. [1] and Meldal et al. [2] in 2002, represents the most efficient essence of “click chemistry” proposed by Sharpless et al. [3] in 2001. This reaction has been widely applied in medicinal, bioorganic, and materials chemistry, as well as many other areas of research over the last decade [4,5]. Although the $CuSO_4$/sodium ascorbate system is still the most frequently used method, numerous efficient catalysts have been developed for improving the present reaction conditions [6]. For example, the use of ligands decreases the amount of Cu catalyst needed and enhances its catalytic activity owing to stabilization of the Cu(I) center [7–14]. Moreover, various Cu complexes, especially Cu(I) complexes bearing different ligands such as amines [7,8], N-heterocycles [9–11], N-heterocycle carbenes (NHCs) [12], phosphines, and phosphonites [13,14], have been developed and have shown satisfactory results. Complexes of other metals such as Ru [15], Ag [16], and Ln [17] can also promote the 1,3-dipolar cycloaddition reaction to generate triazoles. In addition, several recyclable heterogeneous catalysts have been reported in recent years [18].

The ligands most frequently used in 1,3-dipolar cycloaddition reaction between alkynes and azides are symmetrical polydentate nitrogen ligands such as *tris*-(benzyltriazolylmethyl)amine (TBTA) [19,20]. Recently, we found that transi-

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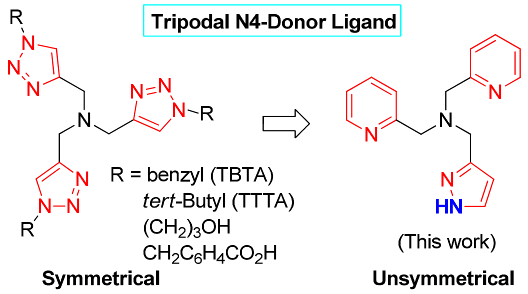
This work was supported by the China Postdoctoral Science Foundation (2013M541254), the National Natural Science Foundation of China (21502120), the Program for Innovative Research Team of the Ministry of Education and the Program for Liaoning Innovative Research Team in University.

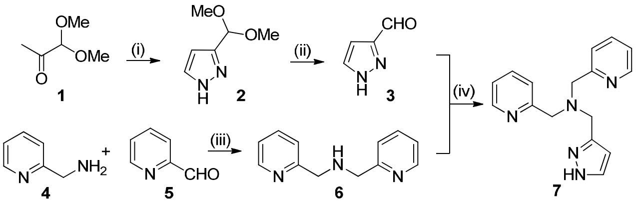
DOI: 10.1016/S1872-2067(15)61121-4 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 37, No. 9, September 2016



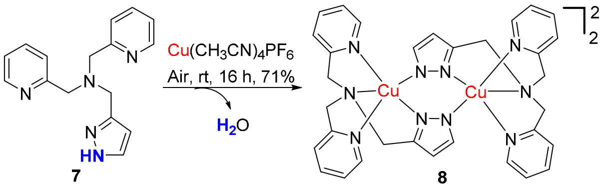
Scheme 1. Ligand bearing an NH group.

tion-metal complex catalysts with pyrazole and benzimidazole ligands containing an NH moiety could significantly accelerate the reaction rate [21,22]. In this paper, we synthesize a highly active binuclear Cu catalyst bearing an unsymmetrical bipyridine-pyrazole-amine ligand and investigate its catalytic activity on the 1,3-dipolar cycloaddition reaction between alkynes and azides. As far as we known, this is one of a few examples of the CuAAC reaction using a binuclear Cu complex as a catalyst [9,12,23,24]. The ligand is shown in Scheme 1.

The ligand was a known compound reported by Reedijk's group [25] and was synthesized through improved methods (Scheme 2). Acetal **1** was treated with *N*,*N*-dimethylformamide dimethyl acetal under reflux and the resulting intermediate was condensed with hydrazine hydrate to produce pyrazole **2** [26]. Pyrazole **2** was deprotected using acetic acid (AcOH) to yield pyrazolyl carboxaldehyde **3** [26]. Amine **6** was prepared from aldehyde **5** and amine **4** [27]. The condensation of **3** and **6** in CH_2Cl_2, followed by reduction with $NaBH(OAc)_3$ gave the ligand **7** (HNpy2pz) [28]. With the aim of obtaining a highly active Cu(I) complex catalyst, $Cu(CH_3CN)_4PF_6$ was chosen as the Cu precursor, which was reacted with ligand **7**. To a MeOH (10 mL) solution of ligand **7** (2.5 mmol, 0.686 g) an equimolar amount of $Cu(CH_3CN)_4PF_6$ (2.5 mmol, 0.915 g) in MeOH (40 mL) was added with stirring. The solution was stirred at room temperature for 16 h in air. The final green solution was concentrated to give a green powder. The product was recrystallized from CH_3CN-hexane-Et_2O (1:1:3) to obtain green crystals. The crystals were collected by filtration, washed with hexane and dried *in vacuo* (0.870 g, 71% yield). Crystals suitable for X-ray diffraction were obtained by layering hexane/Et_2O over an acetonitrile solution at 2–6 °C. HRMS: Calcd. for $C_{32}H_{32}Cu_2F_6N_{10}P_1$ $[M-PF_6^-]^+$: 827.1045; Found: 827.1040. The X-ray crystallographic files, in CIF format, are available from the Cambridge crystallographic data center upon quoting the deposition number CCDC 1444219. To our surprise, a binuclear Cu(II) complex **8** was obtained instead of the designed Cu(I) complex, whereby the Cu(I) center was oxidized to Cu(II) by air in the presence of the NH group in the pyrazole (Eq. (1)). The unit cell of **8** contained a dinuclear cation $[Cu(Npy_2pz)]_2^{2+}$, and the corresponding anions were two PF_6^- which were omitted for clarity (Fig. (1)). Reedijk's group [25] had reported a similar binuclear complex in which ClO_4^- was an anion instead of PF_6^-.



Scheme 2. Synthesis of tripodal N4 ligand 7. (i) a. *N*,*N*-dimethylformamide dimethyl acetal, reflux, 3 h; b. $NH_2NH_2\cdot H_2O$, 40 °C, 18 h, 61% for two steps. (ii) AcOH/H_2O (1:4), 0 °C, 9 h, 53%. (iii) $NaBH_4$, MeOH, rt, overnight, 73%. (iv) $NaBH(OAc)_3$ (3.0 eq.), CH_2Cl_2, rt, 48 h, 51%.



(1)

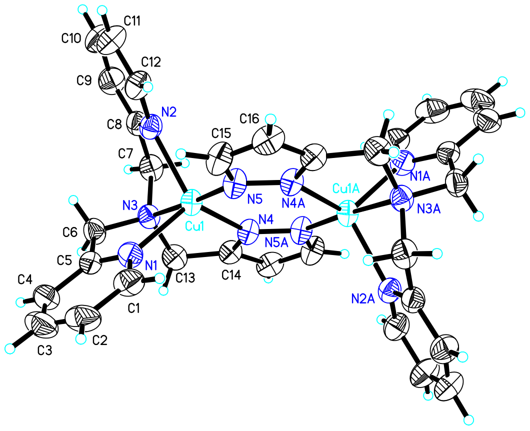
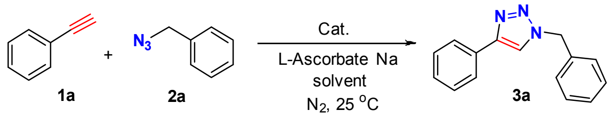


Fig. 1. The molecular structure of **8**.

The catalytic performance of the binuclear complex **8** was investigated and the 1,3-dipolar cycloaddition reaction between phenylacetylene and benzyl azide was selected as the model reaction for exploring the optimal conditions (Table 1). First, different solvents were screened and it was found that MeOH was a suitable solvent. The reaction gave poor results if water, toluene, or even CH_2Cl_2 were used as solvents, maybe because of the poor solubility of catalyst **8** in them (Table 1, entries 1–3). The catalyst loading was then screened and 0.1 mol% loading gave the highest yield of 99% after 16 h (Table 1,

Table 1
Cycloaddition reaction between phenylacetylene and benzyl azide.



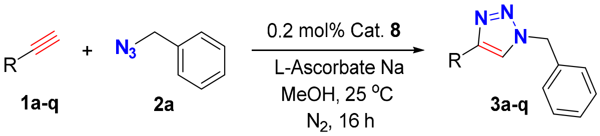
Entry	Cat. (mol%)	NaAsc (mol%)	Solvent	Time (h)	Isolated yield (%)
1	**8** (0.1)	1	CH_2Cl_2	16	6
2	**8** (2)	10	toluene	16	52
3	**8** (0.1)	1	H_2O	16	17
4	**8** (0.1)	1	MeOH	16	99
5	**8** (0.1)	1	MeOH	12	96
6	**8** (0.05)	1	MeOH	12	34
7	**8** (2)	—	MeOH	16	trace

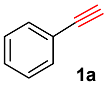
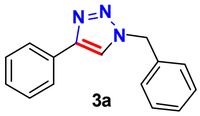
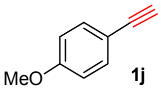
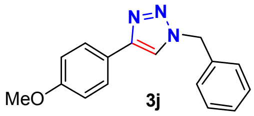
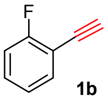
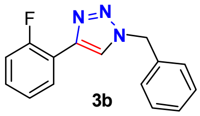
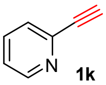
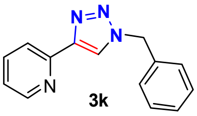
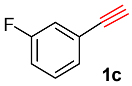
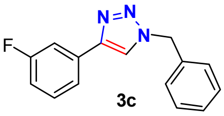
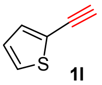
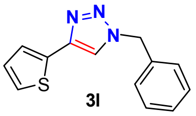
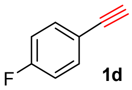
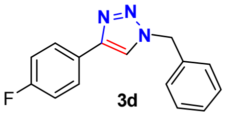
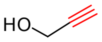
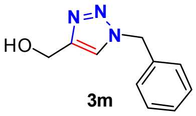
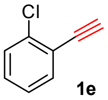
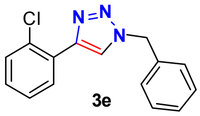
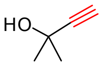
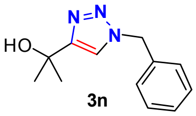
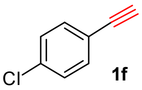
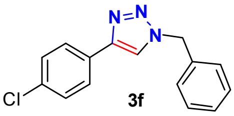
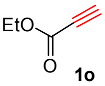
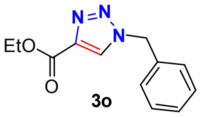
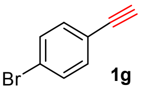
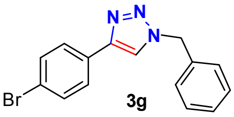
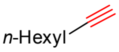
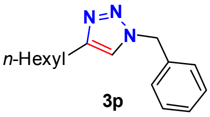
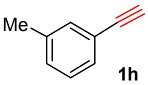
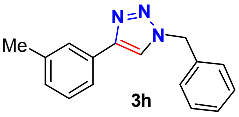
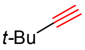
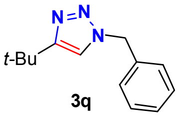
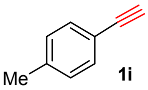
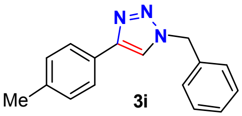
Reaction conditions: phenylacetylene 1.0 mmol, benzyl azide 1.0 mmol, solvents 1.5 mL, N_2, 25 °C.

entry 4). The Cu(II) complex-**8**-catalyzed 1,3-dipolar cycloaddition reaction between phenylacetylene and benzyl azide did not work in the absence of sodium L-ascorbate (Table 1, entry 7). This was consistent with the reported results that Cu(I) was the real active catalyst [5]. Moreover, to avoid the oxidation of the Cu(I) catalyst by air, the cycloaddition reaction should be performed under a N_2 atmosphere. A reaction in air did not give the expected 1,4-diphenyl triazole product.

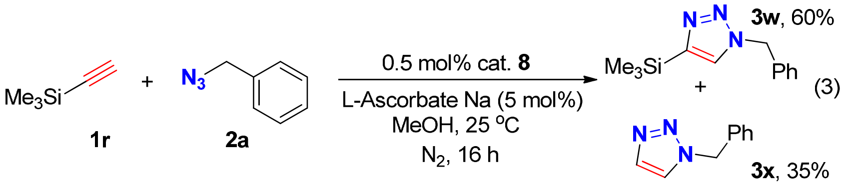
Next, the CuAAC reactions between various alkynes (**1a**–**q**) and benzyl azide (**2a**) were explored under the optimal conditions (Table 2). Phenylacetylene, 3-fluorophenyl, 4-chlorophenyl, and *n*-hexyl acetylene substrates showed the highest reactivity. At 0.1 mol% catalyst loading, their corresponding triazoles were obtained in more than 99% yields (Table 2, entries 1, 3, 6, and 16). Using 0.2 mol% of catalyst, the other halogeno- and methyl-phenylacetylene substrates gave the products in more than 95% yields (Table 2, entries 2, 4, 5, and 7–9). The electron-rich alkyne needed a higher catalyst loading of 0.3 mol%, which gave a 99% yield (Table 2, entry 10). The heterocycle alkynes also showed excellent reactivity, giving 99% and 97% yields (Table 2, entries 11 and 12). We were pleased that the catalytic activity was not affected by the hydroxyls on the substrate. The reaction of propargyl alcohol with benzyl azide produced the corresponding 1,4-disubstituted triazole in 96% yield (Table 2, entry 13). Both alcohol **1n** and the ester **1o** gave 99% yields but they needed a 0.3-mol% cata-

Table 2
The Cu catalyzed 1,3-dipolar cycloaddition reaction of various alkynes.

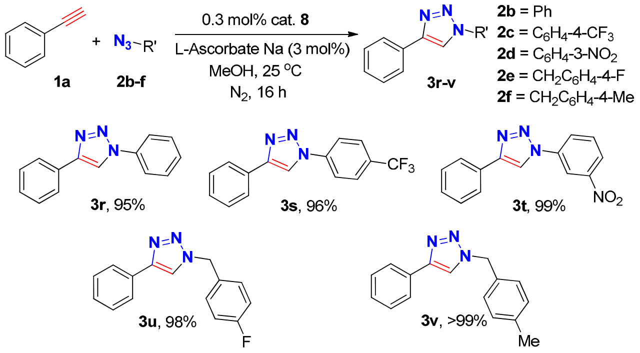


Entry	Alkyne	Product	Isolated yield (%)	Entry	Alkyne	Product	Isolated yield (%)
1[a]	 **1a**	 **3a**	99	10[b]	 **1j**	 **3j**	99
2	 **1b**	 **3b**	96	11	 **1k**	 **3k**	99
3[a]	 **1c**	 **3c**	>99	12	 **1l**	 **3l**	97
4	 **1d**	 **3d**	97	13	 **1m**	 **3m**	96
5	 **1e**	 **3e**	>99	14[b]	 **1n**	 **3n**	99
6[a]	 **1f**	 **3f**	>99	15[b]	 **1o**	 **3o**	99
7	 **1g**	 **3g**	95	16[a]	 **1p**	 **3p**	>99
8	 **1h**	 **3h**	98	17[b,c]	 **1q**	 **3q**	97
9	 **1i**	 **3i**	>99				

Reaction conditions: alkynes 1.0 mmol, benzyl azide 1.0 mmol, Cat. **8** (0.2 mol%), sodium L-ascorbate 2 mol%, MeOH 1.5 mL, N_2, 25 °C, 16 h.
[a] Cat. **8** 0.1 mol%, sodium L-ascorbate 1 mol%. [b] Cat. **8** 0.3 mol%, sodium L-ascorbate 3 mol%. [c] **1q** is 1.2 mmol.



Scheme 4. Cycloaddition reaction between trimethylsilylacetylene and benzyl azide.



Scheme 3. Cu-catalyzed 1,3-dipolar cycloaddition reaction of various azides.

lyst loading owing to the increased steric hindrance (Table 2, entries 14 and 15). For the same reason, *tert*-butylacetylene gave **3q** in 97% yield at 0.3 mol% catalyst loading (Table 2, entry 17).

CuAAC reactions between phenylacetylene and several azides were also investigated. In general, the aryl-substituted azides showed slightly lower reactivity than the benzyl azides. The reactions of five azides (**2b–f**) were performed with 0.3 mol% catalyst loading and the corresponding 1,4-disubstituted triazoles were obtained in isolated yields above 95% (Scheme 3). The CuAAC reaction of trimethylsilyl-acetylene with phenyl azide was an interesting anomaly which gave a normal 1,4-disubstituted triazole **3w** and a non-TMS-containing product **3x** in 60% and 35% yields, respectively (Scheme 4). Fletcher at al. [29] and Sahoo at al. [30] have reported a $SiMe_3$-deprotection reaction in which they needed a base additive such as K_2CO_3.

In conclusion, a binuclear Cu(II) complex bearing an unsymmetrical bipyridine-pyrazole-amine ligand was synthesized from a Cu(I) precursor in air. The complex was an excellent catalyst in the CuAAC reaction between alkynes and azides; at a catalyst loading of 0.1–0.3 mol% all of the 1,4-disubstituted triazoles were obtained in isolated yields above 95%.

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Graphical Abstract

Chin. J. Catal., 2016, 37: 1446–1450 doi: 10.1016/S1872-2067(15)61121-4

Highly active binuclear Cu(II) catalyst bearing an unsymmetrical bipyridine-pyrazole-amine ligand for the azide-alkyne cycloaddition reaction

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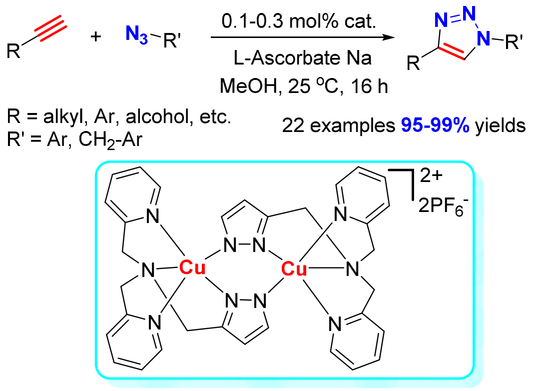

Binuclear Cu(II) complex bearing an unsymmetrical bipyridine-pyrazole-amine ligand was synthesized. The complex was an excellent catalyst in the CuAAC reaction. At 0.1–0.3 mol% catalyst loading all the 1,4-disubstituted triazoles were obtained in 95–99% isolated yields.

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