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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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ABSTRACT

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 H₂O. 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.

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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 CuSO₄/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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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 know, 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 $\text{NaBH}(\text{OAc})_3$ gave the ligand **7** (HNpy_2pz) [28]. With the aim of obtaining a highly active Cu(I) complex catalyst, $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ 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 $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ (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 $\text{C}_{32}\text{H}_{32}\text{Cu}_2\text{F}_6\text{N}_{10}\text{P}_1$ $[\text{M}-\text{PF}_6]^{+}$: 827.1045; Found: 827.1040. The X-ray crystallographic files, in CIF format, are available from the Cambridge crystallographic data center upon quoting the

Scheme 2. Synthesis of tripodal N4 ligand **7**. (i) a. *N,N*-dimethylformamide dimethyl acetal, reflux, 3 h; b. $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, 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) $\text{NaBH}(\text{OAc})_3$ (3.0 eq.), CH_2Cl_2 , rt, 48 h, 51%.

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

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 $[\text{Cu}(\text{Npy}_2\text{pz})]^{2+}$, 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^- .

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.

Reaction scheme showing the synthesis of **3a** from **1a** and **2a** using a catalyst (Cat.), L-Ascorbate Na, solvent, and N_2 at 25°C .

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 N₂ 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			99	10 ^b			99
2			96	11			99
3 ^a			>99	12			97
4			97	13			96
5			>99	14 ^b			99
6 ^a			>99	15 ^b			99
7			95	16 ^a			>99
8			98	17 ^{b,c}			97
9			>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, N₂, 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 et al. [29] and Sahoo et al. [30] have reported a

SiMe₃-deprotection reaction in which they needed a base additive such as K₂CO₃.

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

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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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含有非对称型双吡啶甲基吡唑甲基胺配体的高活性双核铜配合物 催化叠氮与炔烃环加成反应

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摘要: Cu(I)催化的炔烃与叠氮的 Huisgen 1,3-偶极环加成反应 (CuAAC) 可用于构建三唑环, 该反应条件温和, 产物专一, 被认为是“点击化学”的精髓, 并广泛应用于医药、生物有机及材料化学等多个领域。CuSO₄/抗坏血酸钠体系是该反应最常用的催化方法, 但近年来, 大量更高效的催化体系被成功开发以解决当前催化体系中存在的问题, 例如, 外加配体的使用可以明显加快反应速率, 从而降低催化剂量和缩短反应时间, 这归因于配体参与配位可以更好地稳定 Cu(I) 催化中心。目前应用于该反应体系的配体大多为对称型多齿氮配体, 例如三三唑甲胺衍生物 (TBTA) 等。

我们开发了两类含有吡唑、苯并咪唑等基团的非对称型多齿氮配体及其应用, 发现这类配体除了具有稳定金属中心的作用外, 还因有吡唑或苯并咪唑等基团的存在, 所形成的配合物往往比那些包含对称型配体的配合物表现出更高的催化活性。

本文合成了一类含有非对称型配体的铜配合物。将铜前体 Cu(CH₃CN)₄PF₆ 与非对称型多齿氮配体二吡啶甲基吡唑甲基胺 (HNpy₂pz) 在甲醇中反应, 由于配体结构中吡唑 NH 基团的存在, 反应在最终脱除一分子 H₂O 后, 意外获得了一种双核结构的铜配合物, 其分子结构通过 X射线单晶衍射成功表征。受到两个金属中心协同效应的影响, 双核配合物催化剂往往能表现出比单核配合物更优异的催化性能, 因此, 我们进一步考察了该双核配合物催化 CuAAC 反应的活性。结果表明, 在催化剂量低至 0.1–0.3 mol% 的情况下, 22 种炔烃和叠氮在 25 °C 反应 16 h 均能得到单一的 1,4-二取代三唑产物, 分离收率在 95% 以上, 且抗坏血酸钠还原剂量仅需 1–3 mol%, 说明受到配体的影响, 催化剂的稳定性非常好。这是目前该反应成功开发出的几个高效双核催化剂之一。

关键词: 氮杂环配体; 铜配合物; 1,3-偶极环加成; 炔烃; 叠氮

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