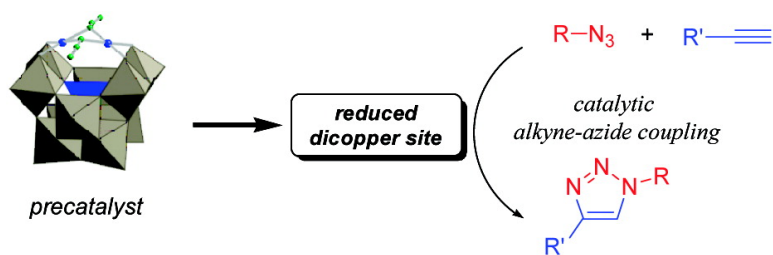


## 1,3-Dipolar Cycloaddition of Organic Azides to Alkynes by a Dicopper-Substituted Silicotungstate

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## 1,3-Dipolar Cycloaddition of Organic Azides to Alkynes by a Dicopper-Substituted Silicotungstate

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**Abstract:** The dicopper-substituted  $\gamma$ -Keggin silicotungstate  $\text{TBA}_4[\gamma\text{-H}_2\text{SiW}_{10}\text{O}_{36}\text{Cu}_2(\mu\text{-}1,1\text{-N}_3)_2]$  (**I**, TBA = tetra-*n*-butylammonium) could act as an efficient precatalyst for the regioselective 1,3-dipolar cycloaddition of organic azides to alkynes. Various combinations of substrates (four azides and eight alkynes) were efficiently converted to the corresponding 1,2,3-triazole derivatives in excellent yields without any additives. The present system was applicable to a larger-scale cycloaddition of benzyl azide to phenylacetylene under solvent-free conditions (100 mmol scale) in which 21.5 g of the analytically pure corresponding triazole could be isolated. In this case, the turnover frequency and the turnover number reached up to  $14\,800\text{ h}^{-1}$  and 91 500, respectively, and these values were the highest among those reported for the copper-mediated systems so far. In addition, **I** could be applied to the one-pot synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole from benzyl chloride, sodium azide, and phenylacetylene. The catalyst effect, kinetic, mechanistic, and computational studies show that the reduced dicopper core plays an important role in the present 1,3-dipolar cycloaddition.

### Introduction

Huisgen 1,3-dipolar cycloaddition of organic azides to alkynes is one of the most important synthetic routes to 1,2,3-triazole derivatives,<sup>1</sup> which have been utilized as dyes, photostabilizers, agrochemicals, and biochemicals.<sup>2</sup> This transformation shows high chemoselectivity because many functional groups do not react with azides or alkynes. However, Huisgen cycloaddition usually requires high reaction temperature (>ca. 353 K) and results in the formation of a mixture of 1,4- and 1,5-regioisomers.<sup>1</sup> In 2002, the groups of Sharpless<sup>3</sup> and Meldal<sup>4</sup> have independently reported that copper catalysts dramatically accelerate the reaction and make it totally regioselective to the 1,4-regioisomer. The copper-catalyzed regioselective 1,3-dipolar cycloaddition ("click reaction") has now been used for the tailor-made syntheses of various complex materials.<sup>5</sup>

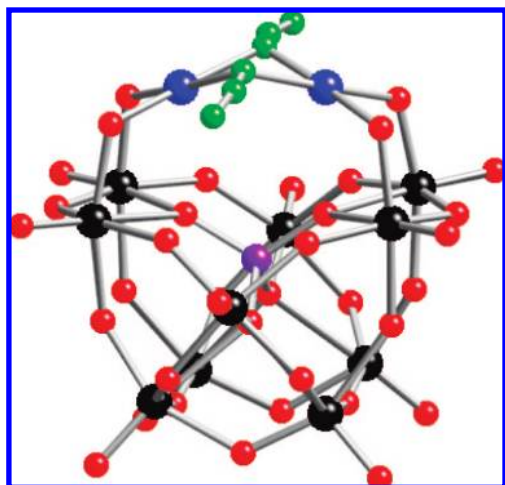
It has been reported that the 1,3-dipolar cycloaddition is catalyzed by copper(I) acetylide species. However, it is still controversial to whether a mononuclear or dinuclear (or more) acetylide species is the active species for the cycloaddition. Some catalytically active mononuclear copper(I) complexes with *N*-heterocyclic carbene, polyamine, and triazole ligands have been isolated and characterized.<sup>5f,m,n</sup> Although the dinuclear copper species has been postulated as a key intermediate on

the basis of kinetic, mechanistic, and theoretical studies,<sup>5c,o-q,6</sup> there are no reports on the 1,3-dipolar cycloaddition by dinuclear copper catalysts.

Interest in the catalysis of metal-substituted polyoxometalates (POMs), which are synthesized by the introduction of substituent

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- (6) Generally, copper(I) acetylide is well-known to prefer at least dinuclear structures with bridging  $\mu$ -acetylide groups. According to the quantum chemical calculations reported by Straub, the dinuclear acetylide species shows higher stability and reactivity for the 1,3-dipolar cycloaddition than the mononuclear species.<sup>5p</sup> In addition, the Gibbs free energy of the mononuclear transition state is equivalent to an overall Gibbs free energy barrier and is significantly higher than that of uncatalyzed cycloaddition.<sup>5p</sup> Finn and co-workers reported that the reaction rate is second-order dependent on the concentration of the copper species under catalytic conditions ( $[\text{alkyne}]/[\text{Cu}] > 2.5$ ).<sup>5c</sup>



**Figure 1.** A ball-and-stick representation of the anion part of **I**. Blue, green, black, purple, and red spheres show the copper, nitrogen (azido), tungsten, silicon, and oxygen atoms, respectively.

metal cations into the vacant site(s) of lacunary POMs, has been rapidly increasing because of the unique reactivity depending on their compositions and structures of active sites.<sup>7</sup> Until now, various kinds of metal-substituted POMs have been synthesized and used as catalysts for various functional group transformations.<sup>7</sup> Very recently, we have reported that the dicopper-substituted  $\gamma$ -Keggin silicotungstate TBA<sub>4</sub>[ $\gamma$ -H<sub>2</sub>SiW<sub>10</sub>O<sub>36</sub>Cu<sub>2</sub>( $\mu$ -1,1-N<sub>3</sub>)<sub>2</sub>] (**I**, TBA = tetra-*n*-butylammonium, Figure 1) shows high catalytic activity for the oxidative alkyne–alkyne homocoupling.<sup>8</sup> In this paper, we report that complex **I** acts as an efficient precatalyst for the regioselective 1,3-dipolar cycloaddition of organic azides to alkynes. The catalyst effect, kinetic, mechanistic, and computational studies support the possible cooperative involvement of a reduced dicopper core in catalyzing the present cycloaddition reaction.

## Results and Discussion

**1,3-Dipolar Cycloaddition of Organic Azides to Alkynes by I.** The 1,3-dipolar cycloaddition of benzyl azide (**1a**) to phenylacetylene (**2a**) in the presence of **I** efficiently proceeded in polar aprotic solvents (**I/1a/2a** = 1:1000:1000, Table 1). Among the solvents tested, acetonitrile was the most effective solvent and the corresponding 1,2,3-triazole **3a** was obtained in 98% yield (entry 1). The reaction rate in air was much slower than that in Ar (entry 2). In contrast, nonpolar and polar protic solvents gave low yields of **3a** (entries 4–9). The use of acetonitrile has a significant advantage of the catalyst/product separation. After the reaction was completed, the analytically pure crystals of **3a** could be isolated in 98% yield (>99% purity, no contamination of metal species) *only by cooling the reaction mixture* (243 K, Figure S1). In addition, the precatalyst could easily be recovered in 94% yield by addition of an excess

**Table 1.** 1,3-Dipolar Cycloaddition of **1a** to **2a**<sup>a</sup>

entry	catalyst	solvent	yield of <b>3a</b> (%)
1	<b>I</b>	acetonitrile	98
2 <sup>b</sup>	<b>I</b>	acetonitrile	13
3	without	acetonitrile	<1
4	<b>I</b>	DMSO	51
5	<b>I</b>	DMF	38
6	<b>I</b>	Toluene	8
7	<b>I</b>	Methanol	6
8	<b>I</b>	Water	4
9	<b>I</b>	1,2-dichloroethane	1
10	TBA <sub>4</sub> [ $\alpha$ -H <sub>2</sub> SiW <sub>11</sub> CuO <sub>39</sub> ]	acetonitrile	1
11 <sup>c</sup>	TBA <sub>4</sub> [ $\gamma$ -SiW <sub>12</sub> O <sub>40</sub> ]	acetonitrile	2
12 <sup>d</sup>	TBA <sub>4</sub> [ $\gamma$ -SiW <sub>10</sub> O <sub>34</sub> (H <sub>2</sub> O) <sub>2</sub> ] + CuCl <sub>2</sub> + NaN <sub>3</sub>	acetonitrile	28
13 <sup>d</sup>	TBA <sub>3</sub> [ $\alpha$ -PW <sub>12</sub> O <sub>40</sub> ] + CuCl <sub>2</sub> + NaN <sub>3</sub>	acetonitrile	7
14 <sup>d</sup>	TBA <sub>4</sub> [ $\alpha$ -SiW <sub>12</sub> O <sub>40</sub> ] + CuCl <sub>2</sub> + NaN <sub>3</sub>	acetonitrile	10
15 <sup>d</sup>	TBA <sub>4</sub> [ $\gamma$ -SiW <sub>12</sub> O <sub>40</sub> ] + CuCl <sub>2</sub> + NaN <sub>3</sub>	acetonitrile	10
16 <sup>d</sup>	TBA <sub>4</sub> H <sub>4</sub> [ $\alpha$ -SiW <sub>11</sub> O <sub>39</sub> ] + CuCl <sub>2</sub> + NaN <sub>3</sub>	acetonitrile	<1
17 <sup>d</sup>	TBA <sub>3</sub> H <sub>7</sub> [ $\alpha$ -SiW <sub>9</sub> O <sub>34</sub> ] + CuCl <sub>2</sub> + NaN <sub>3</sub>	acetonitrile	<1
18 <sup>e</sup>	CuCl <sub>2</sub> + NaN <sub>3</sub>	acetonitrile	9
19	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	acetonitrile	<1
20	CuCl <sub>2</sub>	acetonitrile	<1
21	Cu(OTf) <sub>2</sub>	acetonitrile	<1
22	CuSO <sub>4</sub> ·5H <sub>2</sub> O	acetonitrile	<1
23	CuCl	acetonitrile	9
24	CuI	acetonitrile	8
25	Cu(C≡CPh)	acetonitrile	3
26	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]PF <sub>6</sub>	acetonitrile	<1
27	[Cu(OTf) <sub>2</sub> ] <sub>2</sub> ·C <sub>6</sub> H <sub>6</sub>	acetonitrile	<1

<sup>a</sup> Reaction conditions: **I** (Cu: 0.2 mol%), **1a** (1.0 mmol), **2a** (1.0 mmol), solvent (1.5 mL), 333 K, 3 h, in 1 atm of Ar. Yields were determined by GC analysis using an internal standard (naphthalene). <sup>b</sup> In 1 atm of air. <sup>c</sup> TBA<sub>4</sub>[ $\gamma$ -SiW<sub>12</sub>O<sub>40</sub>] (0.1 mol%). <sup>d</sup> Polyoxometalate (0.1 mol%), CuCl<sub>2</sub> (0.2 mol%), NaN<sub>3</sub> (0.2 mol%). <sup>e</sup> CuCl<sub>2</sub> (0.2 mol%), NaN<sub>3</sub> (0.2 mol%).

amount of toluene (precipitation method; see Experimental Section) to the reaction solution. The recovered precatalyst could be reused at least three times without loss of its catalytic activity and selectivity (entries 2–4 in Table 2). As shown in Table 1, the reaction hardly proceeded in the absence of the catalysts (entry 3) or in the presence of simple copper(I) and copper(II) salts under the same conditions (entries 19–27). The reactivity of a mixture of CuCl<sub>2</sub> and NaN<sub>3</sub> for the cycloaddition was enhanced by the addition of  $\gamma$ -Keggin-type divacant silicotungstate TBA<sub>4</sub>[ $\gamma$ -SiW<sub>10</sub>O<sub>34</sub>(H<sub>2</sub>O)<sub>2</sub>] (entry 12), while a mixture of CuCl<sub>2</sub> and NaN<sub>3</sub> was almost inactive (entry 18). On the other hand, such an acceleration was not observed by addition of other POMs (entries 13–17), suggesting that the divacant  $\gamma$ -Keggin anion is a specific ligand for the present cycloaddition.

In the presence of a reducing agent (sodium ascorbate, one equiv with respect to **I**), the cycloaddition of **1a** to **2a** efficiently proceeded at 303 K to give **3a** in 98% yield and the turnover frequency (TOF) reached up to 370 h<sup>-1</sup> (eq 1). The TOF was higher than those (0.2–120 h<sup>-1</sup>) of the copper catalysts (except for [(SIMes)CuBr] (408 h<sup>-1</sup>)<sup>5f,9</sup>) with reducing agents and/or nitrogen bases such as *N*-heterocyclic carbene, phenanthroline, and tris(triazolyl)amine additives at ambient temperature (see

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**Table 2.** 1,3-Dipolar Cycloaddition of Various Organic Azides to Alkynes<sup>a</sup>

$$\text{R-N}_3 \quad + \quad \text{R}'\text{-C}\equiv\text{C} \quad \longrightarrow \quad \text{Triazole} \quad \text{3}$$

**1**
**2**
**3**

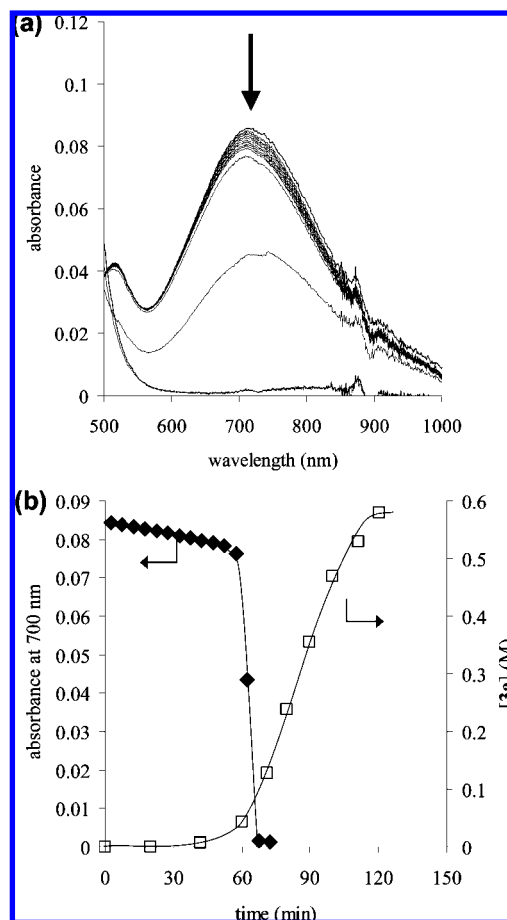
entry	azide (R =)	alkyne (R' =)	triazole	time (h)	yield <sup>b</sup> (%)
1	Bn ( <b>1a</b> )	Ph ( <b>2a</b> )	<b>3a</b>	3	98
2 <sup>c</sup>	<b>1a</b>	<b>2a</b>	<b>3a</b>	2	98
3 <sup>c</sup>	<b>1a</b>	<b>2a</b>	<b>3a</b>	2	99
4 <sup>c</sup>	<b>1a</b>	<b>2a</b>	<b>3a</b>	2	99
3	<b>1a</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	<b>3b</b>	1.5	90
4	<b>1a</b>	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	<b>3c</b>	2.5	97
5	<b>1a</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	<b>3d</b>	2	94
6	<b>1a</b>	4-FC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	<b>3e</b>	3	91
7	<b>1a</b>	3-ClC <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )	<b>3f</b>	5	89
8 <sup>d</sup>	<b>1a</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub> ( <b>2g</b> )	<b>3g</b>	10	93
9 <sup>d</sup>	<b>1a</b>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>2h</b> )	<b>3h</b>	18	88
10	4-CH <sub>3</sub> Bn ( <b>1b</b> )	<b>2a</b>	<b>3i</b>	2.5	90
11	<b>1b</b>	<b>2b</b>	<b>3j</b>	1.5	88
12 <sup>d</sup>	adamantyl ( <b>1c</b> )	<b>2a</b>	<b>3k</b>	5	95
13 <sup>d</sup>	<b>1c</b>	<b>2e</b>	<b>3l</b>	4	94
14	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ( <b>1d</b> )	<b>2a</b>	<b>3m</b>	2.5	80
15	<b>1d</b>	<b>2f</b>	<b>3n</b>	2	94
16 <sup>d</sup>	<b>1d</b>	<b>2g</b>	<b>3o</b>	3.5	91

<sup>a</sup> Reaction conditions: **I** (0.1 mol%), **1** (1.0 mmol), **2** (1.0 mmol), acetonitrile (1.5 mL), 333 K, in 1 atm of Ar. <sup>b</sup> Isolated yields. <sup>c</sup> Reuse experiment: first recycle (entry 2), second recycle (entry 3), and third recycle (entry 4). The reaction conditions were the same except that the recovered precatalyst was used. <sup>d</sup> **I** (0.5 mol%).

Table S1). In addition, the present system was applicable to a larger-scale cycloaddition of **1a** to **2a** under *solvent-free conditions* (100 mmol scale) and the analytically pure 21.5 g of **3a** could be isolated (eq 2). In this case, the TOF and the turnover number (TON) reached up to 14 800 h<sup>-1</sup> and 91 500, respectively, and these values were the highest among those reported for the copper-mediated systems so far (TOF: <1–408 h<sup>-1</sup>, TON: 1–1720; see Table S1). The one-pot synthesis of **3a** from benzyl chloride, sodium azide, and **2a** could also be achieved (eq 3).<sup>10b,c,j</sup>

In the presence of **I**, various combinations of organic azides and alkynes were efficiently converted into the corresponding 1,2,3-triazole derivatives in excellent yields without any additives such as reducing agents and nitrogen bases (Table 2). It

- (9) The reaction rate for the [(SImes)CuBr]-catalyzed cycloaddition of **1a** to **2a** in DMSO showed a first-order dependence on the concentration of [(SImes)CuBr] (6.5–50.4 mM, see Supporting Information). In the case of [(SImes)CuBr], the cycloaddition of internal alkynes efficiently proceeded. On the other hand, no cycloaddition of internal alkynes proceeded in the presence of the precatalyst **I**. The discrepancy suggests that the [(SImes)CuBr]-catalyzed cyclization likely proceeds in a different way in comparison with the **I**-mediated cycloaddition.
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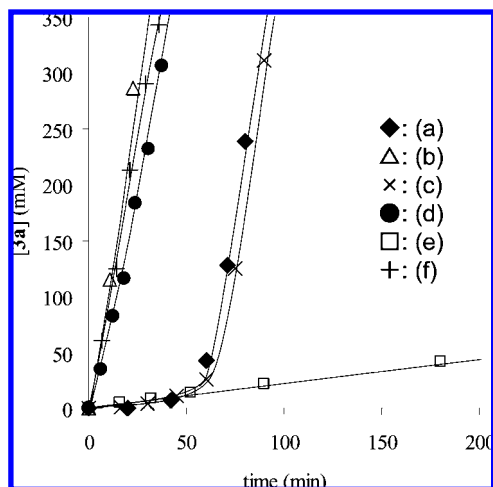


**Figure 2.** (a) Changes of UV–vis spectra (~70 min) for the 1,3-dipolar cycloaddition of **1a** to **2a** in the presence of **I** and (b) time profiles of the absorbance at 700 nm and formation of **3a**. Reaction conditions: **I** (0.58 mM), **1a** (0.58 M), **2a** (0.58 M), acetonitrile (1.5 mL), 333 K, in 1 atm of Ar.

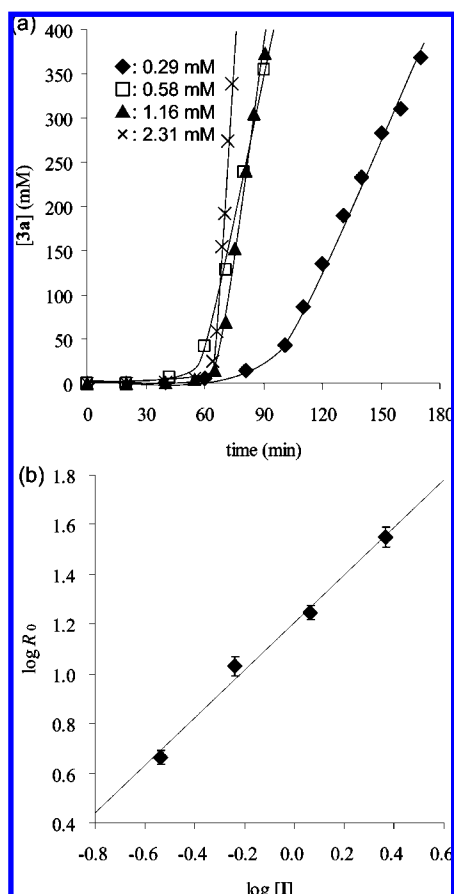
was confirmed by the X-ray crystallographic analyses (Figure S2) and/or NOE experiments that the 1,4-disubstituted-1,2,3-triazoles were formed in a completely regioselective manner without formation of 1,5-regioisomers in all cases. Not only benzylic (**1a** and **1b**) but also aliphatic azides (**1c** and **1d**) gave excellent yields of the corresponding 1,2,3-triazoles. Also, aromatic terminal alkynes (**2a–2f**) as well as aliphatic ones (**2g** and **2h**) worked well as reaction partners of organic azides.

**Role of Dinuclear Copper Site.** The 1,3-dipolar cycloaddition of **1a** to **2a** under the conditions described in Table 1 showed an induction period of ~50 min (Figure 2b). During the induction period, an almost equimolar amount of **2a** with respect to copper(II) species in **I** was converted into 1,4-diphenyl-1,3-butadiyne and the absorption band at 700 nm, which is assignable to the d-d transition of the copper(II) species in **I** (Figure 2a),<sup>11</sup> almost disappeared. These results suggest that all copper(II) species in **I** are reduced to copper(I) species and that the reaction is initiated after the formation of copper(I) species. The idea was supported by the following facts: (1) Upon pretreatment of **I** with **2a** or a reducing agent of ascorbic acid or sodium ascorbate, the 700-nm band intensity greatly decreased and the induction period disappeared (Figure 3b, d, and f). (2) The reaction rates for the cycloaddition of **1a** to **2a** upon pretreatment of **I** with **2a**, ascorbic acid, and sodium ascorbate were  $11.9 \pm 1.4$ ,  $9.7 \pm 1.5$ , and  $10.0 \pm 0.8$  mM min<sup>-1</sup>,



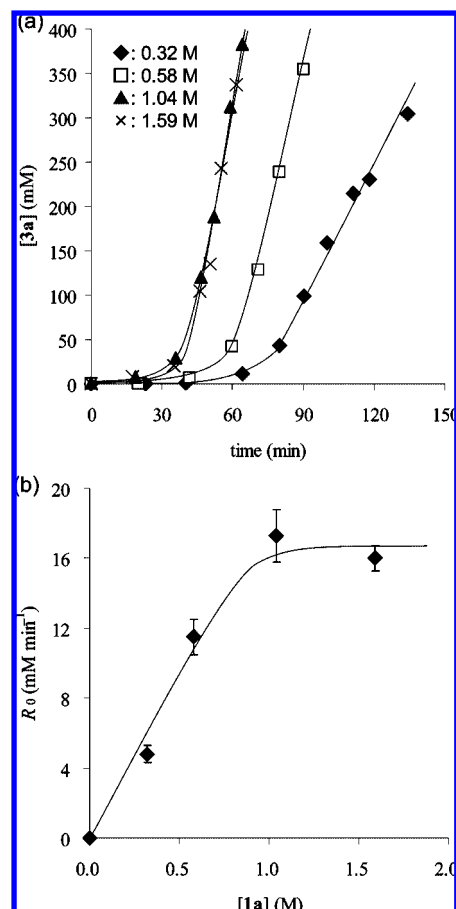


**Figure 3.** Reaction profiles for the 1,3-dipolar cycloaddition of **1a** to **2a**. Reaction conditions: **I** (Cu: 1.16 mM), **1a** (0.58 M), **2a** (0.58 M), acetonitrile (1.5 mL), 333 K, in 1 atm of Ar atmosphere. The profiles show the cycloaddition catalyzed by (a) **I**, (b) **I** pretreated with **2a** at 333 K for 90 min before addition of **1a**, (c) **I** pretreated with **1a** at 333 K for 90 min before addition of **2a**, (d) **I** in the presence of ascorbic acid (0.58 mM, 0.5 equiv with respect to Cu), (e) TBA<sub>4</sub>[ $\alpha$ -H<sub>2</sub>SiW<sub>11</sub>CuO<sub>39</sub>] in the presence of ascorbic acid (0.58 mM, 0.5 equiv with respect to Cu), and (f) **I** in the presence of sodium ascorbate (0.58 mM, 0.5 equiv with respect to Cu) in a mixed solvent of acetonitrile/water (1.48/0.02 mL).



**Figure 4.** (a) Reaction profiles and (b) dependence of the reaction rate on the concentration of **I** for 1,3-dipolar cycloaddition of **1a** to **2a**. Reaction conditions: **I** (0.29–2.31 mM), **1a** (0.58 M), **2a** (0.58 M), acetonitrile (1.5 mL), 333 K, in 1 atm of Ar. Slope = 0.99 ( $R^2 = 0.99$ ).

respectively, and were almost the same as that ( $10.7 \pm 1.1$ ) after the induction period with fresh **I**.

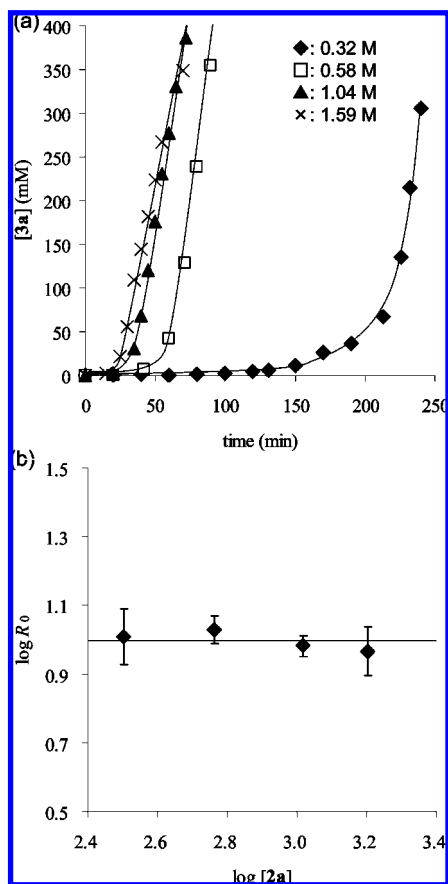


**Figure 5.** (a) Reaction profiles and (b) dependence of the reaction rate on the concentration of **1a** for 1,3-dipolar cycloaddition of **1a** to **2a**. Reaction conditions: **I** (0.58 mM), **1a** (0.32–1.59 M), **2a** (0.58 M), acetonitrile (1.5 mL), 333 K, in 1 atm of Ar.

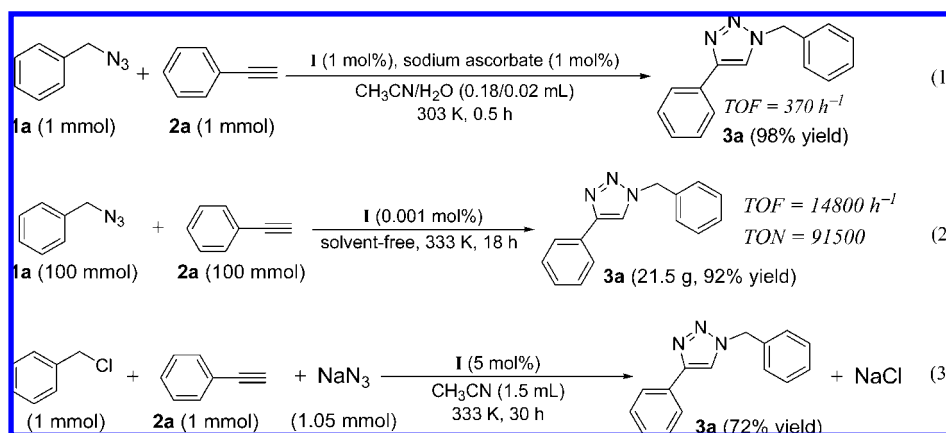
When the recovered precatalyst was used, the induction period disappeared and the reaction proceeded at almost the same rate as that after the induction period with fresh **I** (Figure S3).<sup>12</sup> The catalytic activities of the monocopper-substituted TBA<sub>4</sub>[ $\alpha$ -H<sub>2</sub>SiW<sub>11</sub>CuO<sub>39</sub>] and the noncopper-substituted TBA<sub>4</sub>[ $\gamma$ -SiW<sub>12</sub>O<sub>40</sub>] were much lower than that of **I** (entries 10 and 11 in Table 1). Even in the presence of a reducing agent (ascorbic acid, 0.5 equiv with respect to Cu), TBA<sub>4</sub>[ $\alpha$ -H<sub>2</sub>SiW<sub>11</sub>CuO<sub>39</sub>] with a monocopper site was almost inactive for the 1,3-dipolar cycloaddition (Figure 3e). In addition, the first-order dependence of the reaction rate on the concentration of **I** was observed (Figure 4).<sup>9</sup> These facts suggest that the  $\gamma$ -Keggin structure of **I** during the catalysis is stable and that the reduced dinuclear Cu(I) core plays an important role in the present cycloaddition.<sup>12</sup>

The present 1,3-dipolar cycloaddition of organic azides to alkynes possibly proceeds as follows (Scheme S1): First, the

- (12) After the reaction was completed, the precipitate was recovered by addition of an excess amount of toluene (precipitation method) to the reaction solution. The copper content in the filtrate was less than 1% of that in fresh **I**, indicating that the copper species hardly leaches into the reaction solution. The elemental analysis and <sup>1</sup>H NMR spectrum of the recovered precipitate showed that the recovered **I** consists of one molecule of dicopper-substituted silicotungstate and two molecules of **3a**. The UV–vis spectrum of the recovered **I** agreed well with that of the sum of fresh **I** and **3a**, suggesting that the  $\gamma$ -Keggin structure of the recovered **I** is retained after the cycloaddition. No absorption bands at 700 nm due to the d–d transition of the copper(II) species was observed in the UV–vis spectrum of the recovered **I**, suggesting the presence of the reduced copper(I) species in the recovered **I**.



**Figure 6.** (a) Reaction profiles and (b) dependence of the reaction rate on the concentration of **2a** for 1,3-dipolar cycloaddition of **1a** to **2a**. Reaction conditions: **I** (0.58 mM), **1a** (0.58 M), **2a** (0.32–1.59 M), acetonitrile (1.5 mL), 333 K, in 1 atm of Ar.



alkyne–alkyne homocoupling proceeds on the dicopper(II) site in **I** to form the corresponding diyne and reduced copper(I) species. This step corresponds to the induction period for the present cycloaddition. Then, the copper(I) acetylide species would be formed by the reaction of the copper(I) species with an alkyne followed by the reaction with an azide to form the corresponding 1,2,3-triazole. The reaction rates for the **I**-mediated 1,3-dipolar cycloaddition of **1a** to **2a** showed a first-order dependence on the concentrations of **I** (0.29–2.31 mM) and **1a** (0.32–1.04 M) and were almost independent of the concentration of **2a** (0.32–1.59 M) under the present catalytic conditions (Figures 4–6). No kinetic isotope effects were observed for the 1,3-dipolar cycloaddition of **1a** to **2a** and phenyl-

acetylene- $d_1$  under the conditions in Table 1 ( $k_H/k_D = 1.0 \pm 0.1$ ), showing that the formation of the acetylide species is not included in the rate-limiting step. All the results show that the reaction of the acetylide species with an azide is the rate-limiting step.<sup>5c,o–q</sup>

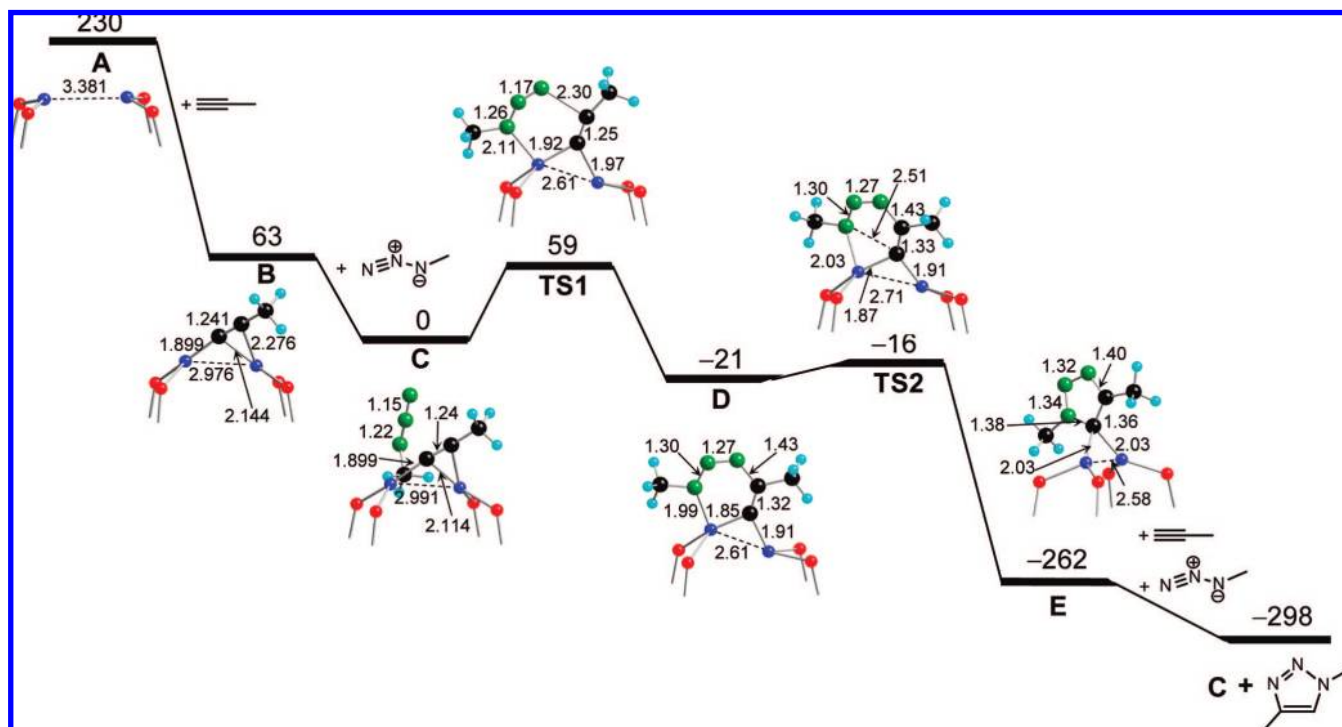
The density functional theory calculations were carried out to confirm the possible cooperative involvement of two copper centers in catalyzing the present cycloaddition reaction. The energies of the reaction steps were calculated with density functional theory according to Scheme S1, and the results are summarized in Figure 7. The formation of the dicopper(I)-alkynyl species containing *one*  $\sigma,\pi$ -bridging acetylide unit (**B**) by the reaction of the dicopper(I) species (**A**) with an alkyne was calculated to be exothermic by  $167 \text{ kJ mol}^{-1}$ . The formation of the dicopper(I)-alkynyl species containing *two*  $\sigma,\pi$ -bridging acetylide units was energetically unfavorable by  $150 \text{ kJ mol}^{-1}$  in comparison with that of **B**. The azide interacts with **B** to form the monoalkynyl monoazido dicopper(I) intermediate (**C**). This step was calculated to be exothermic by  $63 \text{ kJ mol}^{-1}$ . Then, the nucleophilic attack of the terminal nitrogen atom of an azide on the positively charged carbon atom of the acetylide species takes place to form the six-membered dicopper metallacycle intermediate (**D**). This step is the rate-limiting step for the present 1,3-dipolar cycloaddition, and the activation energy (**TS1**) was calculated to be  $59 \text{ kJ mol}^{-1}$ . This value was comparable to those reported for the 1,3-dipolar cycloaddition with dicopper complex of  $\text{Cu}_2\text{L}(\text{C}\equiv\text{CMe})(\text{N}_3\text{Me})^{5\text{o,p}}$  (L = phenanthroline,  $\text{Cl}^-$ ,  $\text{C}\equiv\text{CMe}^-$ , and  $\text{H}_2\text{O}$ ,  $44\text{--}78 \text{ kJ mol}^{-1}$ ) calculated at the B3LYP level. The activation energy (**TS2**) for the formation of the triazolyl-dicopper species (**E**) from **D** was very low. Triazole is eliminated followed by the reaction with an alkyne and an azide, establishing the catalytic cycle. These computational results also support that an alkyne and an organic azide are activated cooperatively by the dinuclear copper site.

## Conclusion

In summary, complex **I** exhibited high catalytic activity for the 1,3-dipolar cycloaddition of organic azides to alkynes without any additives such as reducing agents and nitrogen bases. In addition, the one-pot synthesis of triazole from a halide, sodium azide, and an alkyne could be realized. The kinetic, spectroscopic, mechanistic, and computational investigations showed that the reduced dicopper core plays an important role in the present cycloaddition.

## Experimental Section

**General.** GC analyses were performed on a Shimadzu GC-2014 with a flame ionization detector equipped with a TC-5 capillary



**Figure 7.** Calculated energy diagram of the 1,3-dipolar cycloaddition of methylazide to methyl acetylene on the reduced precatalyst **I** in the gas phase (energies and lengths in  $\text{kJ mol}^{-1}$  and  $\text{\AA}$ , respectively). Blue, black, green, red, and light blue balls represent copper, carbon, nitrogen, oxygen, and hydrogen atoms, respectively. Polyoxotungstate frameworks of  $[\gamma\text{-H}_x\text{SiW}_{10}\text{O}_{32}]^{x-}$  ( $x = 2$  and  $3$  for **A** and the other states, respectively) are omitted for clarity.

column (internal diameter = 0.25 mm, length = 60 m) or an InertCap 5 capillary column (internal diameter = 0.25 mm, length = 60 m). HPLC analyses were performed on an Agilent 1100 series LC with a UV-vis detector using a CAPCELL PAK MG C18 reversed phase column ( $5 \mu\text{m} \times 3 \text{mm} \phi \times 250 \text{mm}$ , SHISEIDO FINE CHEMICALS). Mass spectra were recorded on a Shimadzu GCMS-QP2010 equipped with a TC-5HT capillary column (internal diameter = 0.25 mm, length = 30 m). NMR spectra were recorded at 298 K on a JEOL JNM-EX-270 ( $^1\text{H}$ , 270 MHz and  $^{13}\text{C}$ , 67.8 MHz) spectrometer. IR spectra were measured on a Jasco FT/IR-460 Plus using KBr disks. UV-vis spectra were recorded on a Jasco V-570 spectrometer with a Unisoku thermostatic cell holder (USP-203). Sodium azide and copper salts were obtained from Wako Pure Chemical Industries or Kanto Chemical (reagent grade) and used as received. Acetonitrile, dichloromethane, and toluene (Kanto Chemical) were purified by The Ultimate Solvent System (GlassContour Company).<sup>13</sup> Other solvents and alkynes were obtained from TCI or Aldrich (reagent grade) and purified prior to use.<sup>14</sup> Organic azides were prepared by the nucleophilic substitution of the corresponding alkyl chloride with sodium azide.<sup>15</sup> The dicopper-substituted silicotungstate **I** was synthesized according to the literature procedure (see Supporting Information).<sup>8</sup>

**1,3-Dipolar Cycloaddition of Organic Azides to Alkynes.** A typical procedure for the dipolar cycloaddition of azides to alkynes was as follows: Into a glass vial were successively placed **I** (0.1 mol%), **1a** (1.0 mmol), **2a** (1.0 mmol), and acetonitrile (1.5 mL). The reaction mixture was stirred at 333 K in 1 atm of Ar. The yield was periodically determined by GC analysis. After the reaction was completed, the reaction solution was cooled to 243 K and analytically pure crystals of **3a** appeared (Figure S1). The crystals were isolated from the reaction solution by decantation (98%

isolated yield). Purities of isolated products were determined by  $^1\text{H}$  NMR (>99% in all cases). Toluene (50 mL) was added to the filtrate, and the precipitated precatalyst was recovered by filtration (94% recovery).

The present cycloaddition showed an induction period. Good linearity was observed between the product amount and the reaction time after the induction period (Figures 2–6). When the recovered precatalyst was used, the induction period disappeared and the reaction proceeded at almost the same rate as that after the induction period with fresh **I** (Figure S3). Therefore, the reaction rates ( $R_0$ ) for the kinetic analyses were determined from the slopes of the reaction profiles (conversion vs time plots) after the induction period.

**Quantum Chemical Calculations.** The calculations were carried out at the B3LYP level theory<sup>16</sup> with 6-31G\* basis sets for H, C, N, O, and Si atoms and the double- $\xi$  quality basis sets with effective core potentials proposed by Hay and Wadt<sup>17</sup> for Cu and W atoms. The entire structure of the dicopper-substituted polyoxotungstate was used as a model in the calculations. Methyl azide and methylacetylene were used as model substrates. To minimize the differences in the solvent effect among the intermediates and transition states, protons were added to the polyoxometalate and the total charge of the system was kept  $-4$  throughout the calculations. The geometry of **A** was optimized within the  $C_2$  symmetry restrictions. The geometries of **B**, **C**, **D**, **E**, **TS1**, and **TS2** were optimized without the symmetry restrictions. Transition state structures were searched by numerically estimating the matrix of second-order energy derivatives at every optimization step and by requiring exactly one eigenvalue of this matrix to be negative. For the transition states, the frequency analysis was conducted at the same level at the final geometry. The optimized geometries were shown in Table S3 and Figure S5 (Supporting Information). The

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zero-point vibrational energies were not included. All calculations were performed with the Gaussian03 program package.<sup>18</sup>

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**Supporting Information Available:** Experimental details, data of triazole derivatives **3a–3o**, Tables S1–S3, Scheme S1, and Figures S1–S5. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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