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Ligand-Assisted, Copper(II) Acetate-Accelerated Azide–Alkyne Cycloaddition

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On the occasion of the 10th anniversary of click chemistry

Abstract: Polytriazole ligands such as the widely used tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA), are shown to assist copper(II) acetate-mediated azide–alkyne cycloaddition (AAC) reactions that involve nonchelating azides. Tris(2-{4-[(dimethylamino)methyl]-1*H*-1,2,3-traizol-1-yl}ethyl)-amine (DTEA) outperforms TBTA in a number of reactions. The satisfactory solubility of DTEA in a wide range of polar and nonpolar solvents, including water and toluene, renders it advantageous under copper(II) acetate-mediated conditions. The copper(II) acetate-mediated formation of the three triazolyl groups in a tris(triazolyl)-based ligand occurs sequentially with an inhibitory effect in the last step. The kinetic investigations of the ligand-assisted reactions reveal an interesting mechanistic dependence on the relative affinity of azide and alkyne to copper (II). In addition to expanding the scope of the copper(II) acetate-mediated AAC reactions to include nonchelating azides, this work offers evidence for the mechanistic synergy between the title reaction and the alkyne oxidative homocoupling reaction. The elucidation of the structural details of the polytriazole-ligand-bound reactive species in copper(I/II)-mediated AAC reactions, however, awaits further characterization of the metal coordination chemistry of polytriazole ligands.

Keywords: alkynes · azides · click chemistry · copper acetate · cycloaddition

Introduction

The copper(I)-catalyzed variant of Huisgen cycloaddition of azide and alkyne (CuAAC) is an efficient method for preparing a covalent linkage, a 1,2,3-triazole, between two molecular units.[1,2] Contrary to the thermal cycloaddition, the copper(I)-catalyzed variant affords rapid formation of regiospecific 1,4-disubstituted 1,2,3-triazoles. With its high yields, wide substrate scope, simple reaction and purification conditions, CuAAC is considered a "click reaction" as defined by Kolb, Finn, and Sharpless a decade ago.[3,4] Due to a substantially lowered energy of activation compared to the thermal reaction, the copper(I)-catalyzed reaction proceeds under very mild conditions, typically without the need for elevated temperatures, thus making it ideal for conditionally demanding biological applications.[5]

Our group reported the use of copper(II) acetate ($Cu(OAc)_2$) to promote CuAAC reactions in the absence of an added reducing agent, for example, sodium ascorbate.[6] We hypothesized that the catalytic copper(I) species is generated upon reduction of copper(II) by either an oxidizable solvent such as methanol[7] or the terminal alkyne substrate by means of the oxidative homocoupling reaction.[8] A subset of the azide substrates rapidly convert to triazole products under the $Cu(OAc)_2$-mediated conditions. Those azides, which are termed "chelating azides," contain auxiliary ligands capable of assisting the azido group in binding the copper centre.[9] To expand the substrate scope of the $Cu(OAc)_2$-mediated procedure to include nonchelating azides, we investigated conditions that employ an accelerating ligand.

Polytriazoles were shown to accelerate CuAAC reactions. Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) is a superior accelerating ligand.[10] The acceleratory effect of TBTA and other polytriazole ligands has been attributed to[11,12] 1) its basicity, which helps deprotonate the alkyne to facilitate the formation of copper(I) acetylide; 2) its multi-

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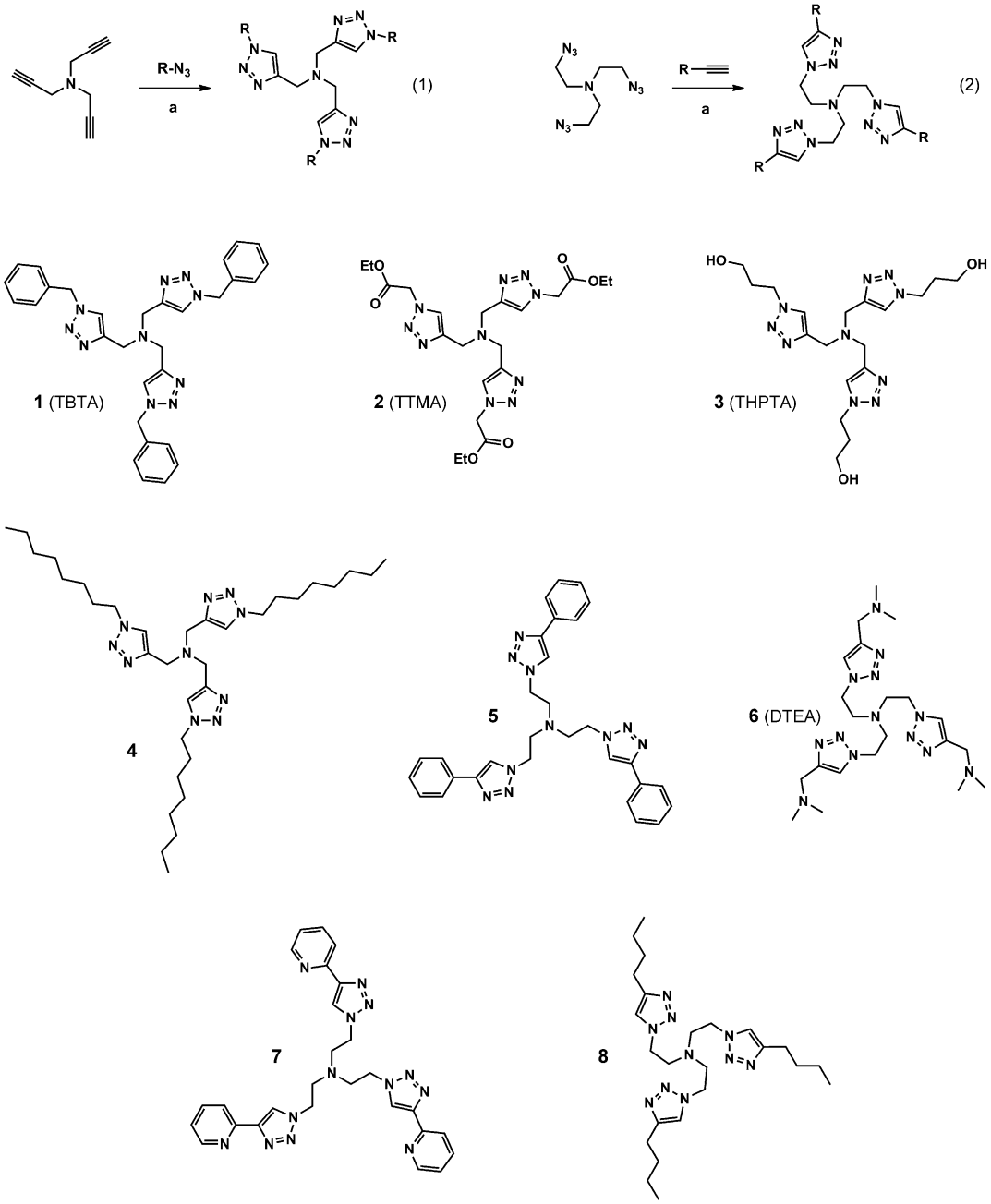
denticity by which the ligand encapsulates and thus protects copper(I) from oxidation by molecular oxygen[13] and prevents the formation of inactive polynuclear copper(I) aggregates; and 3) its coordination lability that allows fast ligand exchange, which is beneficial to catalytic turnover. In the past few years, several other polydentate aza-ligand frameworks have also been found to aid CuAAC reactions.[14–19]

We recently found that TBTA also accelerates $Cu(OAc)_2$-mediated AAC reactions that involve nonchelating azides.[9] In a number of reactions that proceed sluggishly under $Cu(OAc)_2$-mediated conditions, yields of over 90% were achieved in the presence of TBTA within 1 or 2 h. In this work, we investigated the acceleratory effects of other polytriazoles in $Cu(OAc)_2$-mediated AAC reactions. The kinetic studies were also carried out to provide some insights on the mechanistic involvement of TBTA (as an example of polytriazole ligands) under the $Cu(OAc)_2$-mediated conditions.

Results and Discussion

Our previously reported $Cu(OAc)_2$-mediated AAC conditions[6] work exceptionally well to produce various polytriazole ligands, including TBTA (Scheme 1). Tripropargyla-



Scheme 1. Polytriazole ligands synthesized by utilizing the $Cu(OAc)_2$-mediated CuAAC reactions. a) $Cu(OAc)_2$ (5 mol%), CH_3OH, RT.

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mine [Eq. (1) in Scheme 1] and tris(2-azidoethyl)amine [Eq. (2)] serve as the tertiary amino cores and react efficiently with corresponding azide and alkyne substrates, respectively, in CH_3OH with the addition of $Cu(OAc)_2$. In this manner we prepared TBTA (**1**) and its derivatives (**2**–**4**). TBTA (**1**)[10,20] and its analogues TTMA (**2**)[21,22] or THPTA (**3**)[23] accelerate CuAAC reactions under various conditions. The tris(2-azidoethyl)amino core [see Eq. (2), Scheme 1] affords tris(triazolyl)-based ligands **5**–**8** with a different coordination configuration. One of the initial motivations of this work was to compare the reactivities of these two configurations in ligand-assisted CuAAC reactions.

The reactions [e.g., Eqs. (1) and (2) in Scheme 1] to produce polytriazole ligands proceed cleanly and are often accompanied by the release of a significant amount of heat following an induction period (see a video of the formation of tris(2-{4-[(dimethylamino)methyl]-1*H*-1,2,3-traizol-1-yl}ethyl)amine (**6**, DTEA) in the Supporting Information). Purification in most cases only requires an extractive isolation using an aqueous solution of ethylenediaminetetraacetic acid (EDTA), or a treatment with Chelex to remove copper-containing species followed by trituration with either hexanes or diethyl ether. The polytriazole ligands were then used as additives in the $Cu(OAc)_2$-mediated AAC reactions.

The reaction progress of 1-azidooctane and tripropargylamine to afford **4** (**E** in Scheme 2) was monitored by ^{1}H NMR spectroscopy.[24] In this experiment, **A** and **B** are defined as the tripropargylamine and 1-azidooctane substrates, respectively, whereas **C**, **D**, and **E** are mono-, bis-, and tris-triazole product molecules. The reaction proceeds in a stepwise fashion (Figure 1). First, mono-triazole **C** forms and its sharp triazolyl C5−H signal ($\delta = 7.67$ ppm) can be monitored in the aromatic region over the entire course of the reaction. Next, the triazolyl C5−H of bis-triazole **D** can be seen slightly downfield from that of **C**. The increased denticity shall lead to a higher affinity of bis-triazole **D** to copper(I/II) than mono-triazole **C**. The broadened ^{1}H NMR spectroscopic signal of C5−H in **D** can therefore be attributed to the formation of copper(I/II) complex of **D** that equilibrates on the ^{1}H NMR spectroscopic timescale. Finally, tris-triazole **E** emerges with an even further downfield triazolyl C5−H signal that is nearly level with the baseline of the ^{1}H NMR spectrum. The successive broadening and downfield shift of the triazolyl C5−H signal is indicative of the progressively tighter binding to copper(I/II) as tripropargylamine is converted to tris-triazolyl ligand in a stepwise manner.

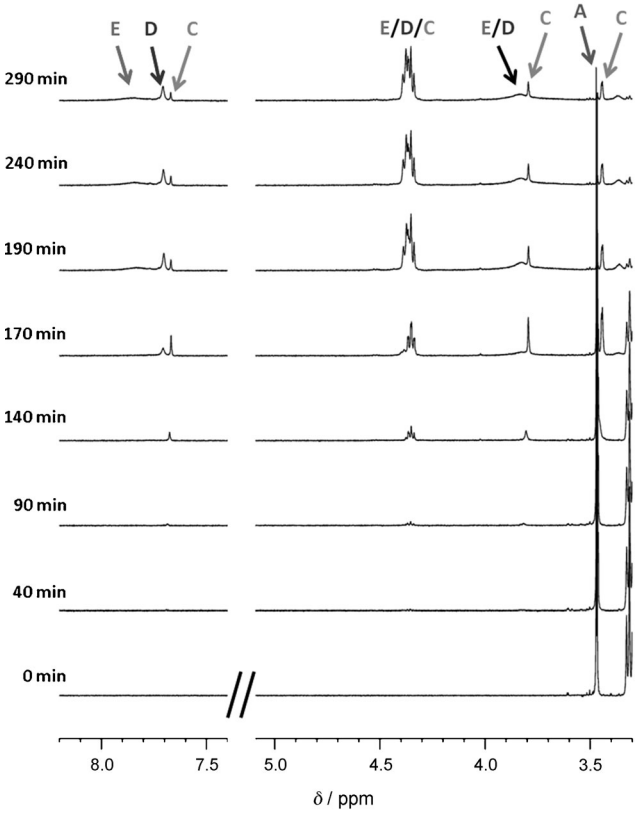
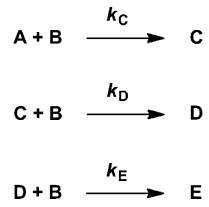
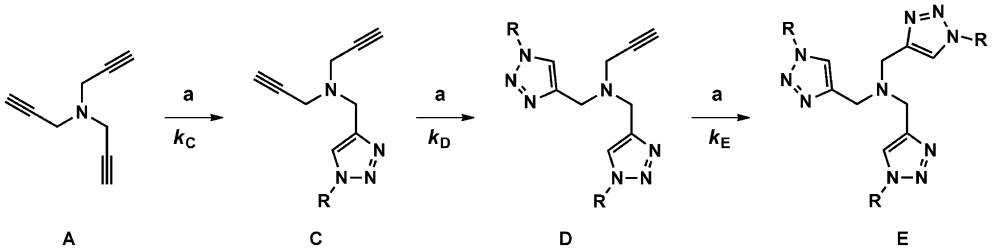


Figure 1. ^{1}H NMR (500 MHz, CD_3CN) spectra of the reaction in Scheme 2 collected over time (from bottom to top). Components **A**, **C**, **D**, and **E** are assigned as indicated by the arrows.

The time courses following the changes of **A**, **C**, **D**, and **E** are shown in Figure 2. An induction period is observed followed by a triazole-producing reaction phase. Mono-triazole **C**, bis-triazole **D**, and tris-triazole **E** form successively. The attempt to fit the kinetic traces using the model in Scheme 3, in which k_C, k_D, and k_E are defined as the apparent second-order rate constants for each step,



Scheme 3. Model used to simulate the time courses shown in Figures 2 and 5.



Scheme 2. Stepwise triazole formation en route to ligand **4** (**E**). R = *n*-octyl; a) $Cu(OAc)_2$ (5 mol%), 1-azidooctane (**B**), CD_3CN, RT. The values of k_C, k_D, and k_E are apparent second-order rate constants in each step.

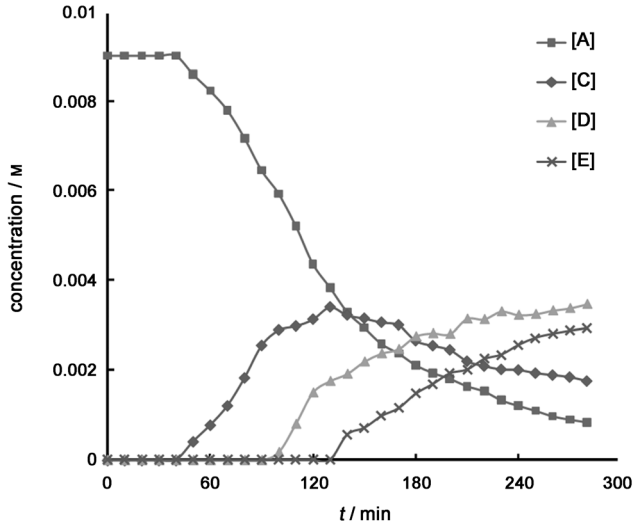


Figure 2. The concentration changes over time of tripropargylamine **A** (square), mono-, bis-, and tris-triazoles **C** (◆), **D** (▲), and **E** (×), respectively, in the reaction in Scheme 2.

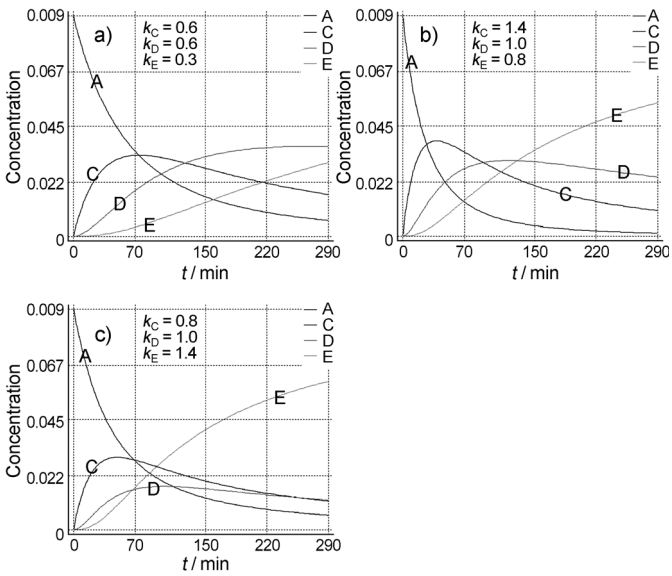
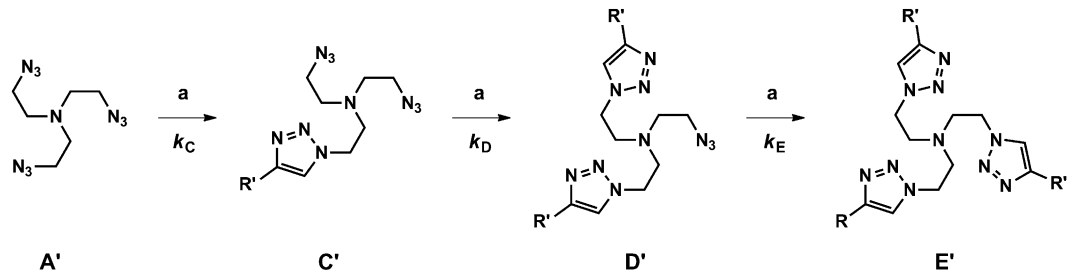


Figure 3. Simulated kinetic traces based on the model in Scheme 3 using different sets of apparent second-order rate constants k_C, k_D, and k_E (listed in the top portions of the figures).

was not successful. We resorted to simulate various kinetic scenarios using the software Pro-Kineticist II (Applied Photophysics). The simulated kinetic traces in Figure 3A resemble the experimental traces of the reaction phases in Figure 2, in which k_C, k_D, and k_E are 0.6, 0.6, 0.3 $M^{-1}min^{-1}$, respectively. The slowest step as simulated is the conversion of bis-triazole **D** to tris-triazole **E** (k_E). Therefore, under the $Cu(OAc)_2$-mediated conditions in this particular case, no autoinductive kinetics were observed, as might have been suspected due to the apparent acceleratory effect of the polytriazoles.[15] The product inhibitory effect as manifested by the lowest rate of the tris-triazole **E** formation allows the accumulation of mono- and bis-triazole intermediates **C** and **D**, which were observed experimentally. We simulated situations in which the last step (k_E) is the fastest as in an autoinductive process (e.g., see Figure 3C). Very little intermediate (**C** and **D**) accumulation would occur in these cases.

Similarly, the reaction between tris(2-azidoethyl)amine **A′** and phenylacetylene **B′** was monitored over time (Scheme 4). The reaction proceeds in a stepwise fashion. The ^1H NMR spectroscopy signals of bis- and tris-triazoles **D′** and **E′** (Figure 4) are significantly sharper than those of their counterparts **D** and **E** in Scheme 2, thus suggesting that copper(II) binds to **D′** and **E′** less tightly than to **D** and **E**. Compared to the reaction to afford **4** (**E**), a much shorter induction period en route to **5** (**E′**) was observed (Figure 5). Furthermore, the AAC reaction appears to be more efficient. The shorter induction period may be attributed to two factors: 1) the inducting oxidative homocoupling reaction is faster because tris(2-azidoethyl)amine is more basic than tripropargylamine and/or phenylacetylene is less sterically hindered than tripropargylamine, and 2) due to the high reactivity that arises from the chelation assistance of tris(azidoethyl)amine,[9] the current reaction requires less copper(I), hence a shorter induction period for its generation, to proceed.

Simulated kinetic traces using the model in Scheme 3 reveal that the experimental traces match well with the scenario of product inhibitory effect (Figure 3B). A product inhibition observed in the syntheses of ligands with both coordination configurations (Schemes 2 and 4) suggests that although the ligands may carry beneficiary effects in CuAAC reactions as outlined in the Introduction, certain portions of copper(I/II) may form unproductive complexes with the ligands.



Scheme 4. Stepwise triazole formation of ligand **5** (**E′**). R′ = phenyl; (a) $Cu(OAc)_2$ (5 mol %), phenylacetylene (**B′**), CD_3CN, rt. k_C, k_D, and k_E are apparent second-order rate constants in each step.

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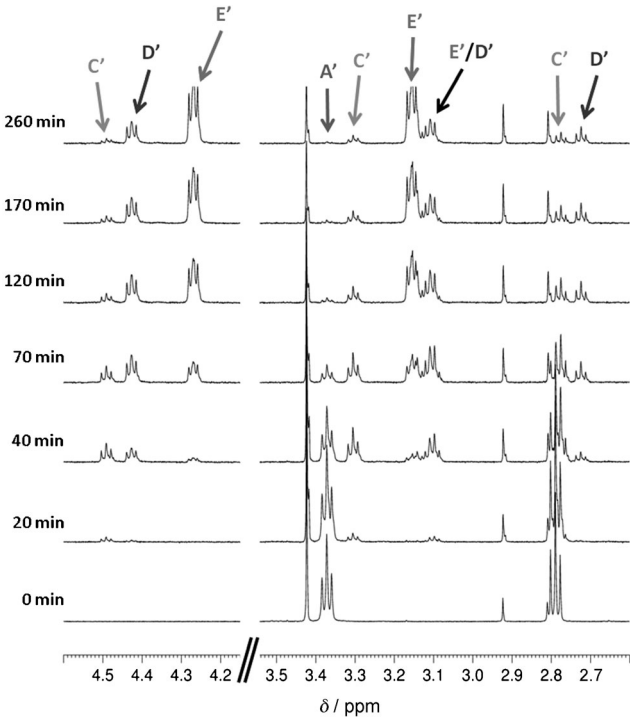


Figure 4. ^{1}H NMR (500 MHz, CD_3CN) spectra of the reaction in Scheme 4 collected over time (from bottom to top). Components **A′**, **C′**, **D′**, and **E′** are assigned as indicated by the arrows.

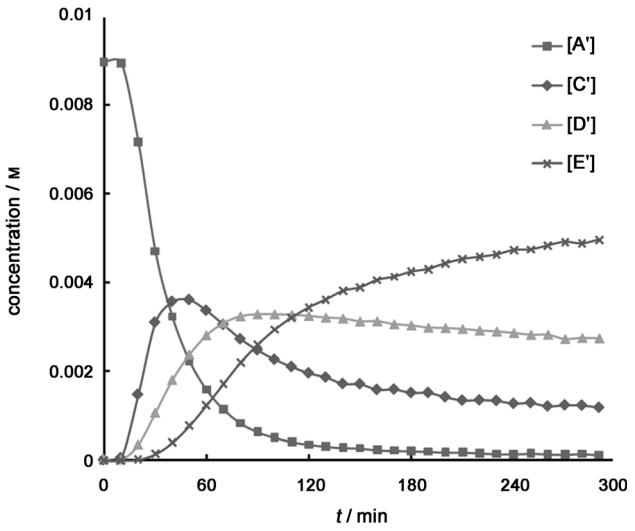


Figure 5. The concentration changes over time of tris(2-azidoethyl)amine **A′**, mono-, bis-, and tris-triazoles **C′**, **D′**, and **E′**, respectively in the reaction in Scheme 4.

Substrate Scope of TBTA-Assisted, $Cu(OAc)_2$-Accelerated AAC Reactions

As previously shown, chelating azides display an accelerating effect in $Cu(OAc)_2$-mediated AAC reactions. To determine whether a ligand would aid reactions that involved nonchelating azides, we screened several azides with different alkyne partners in the presence and absence of TBTA in *t*BuOH (Table 1).

Both aromatic (Table 1, entries 1–5) and aliphatic (entries 6–10) alkyne substrates are included. 2-Picolylazide represents chelating azides with a copper(I/II)-binding auxiliary, whereas benzylazide lacks the chelating ability. 1-Azidooctane was chosen to represent sterically unhindered aliphatic azides. *p*-Azidophenylmethylalcohol represents aromatic azides.

In Table 1, the entries where TBTA does not exert a significant acceleratory effect include reactions that involve 2-picolylazide, *N*,*N*-diethylpropargylamine, and 3,3-dimethylbutyne. 2-Picolylazide reacts rapidly through the chelation-assisted pathway. The strongly basic *N*,*N*-diethylpropargylamine (entry 7) also rapidly converts in the absence of TBTA, possibly due to the formation of a bidentate triazole product that slows down the detrimental aggregation process of copper(I) catalytic species. The *tert*-butyl group in 3,3-dimethylbutyne creates a severe steric effect that is difficult to overcome under the tested conditions. TBTA aids the $Cu(OAc)_2$-mediated AAC reactions of other azide/alkyne combinations, in particular reactions that involve aromatic azides. In the absence of TBTA, *p*-azidobenzylalcohol is almost inactive under $Cu(OAc)_2$-mediated conditions.

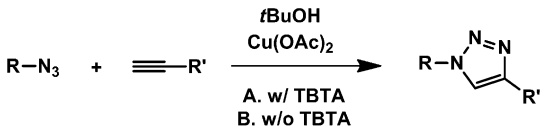
Effect of Other Polytriazole Ligands in $Cu(OAc)_2$-Mediated AAC Reactions

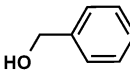
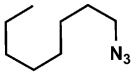
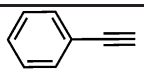
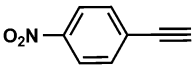
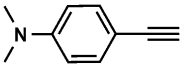
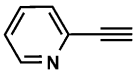
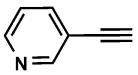
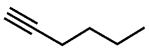
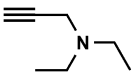
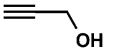
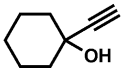
Several reactions from the substrate screening were chosen to assess the acceleratory effects of other polytriazole ligands and triethylamine (TEA) on the $Cu(OAc)_2$-mediated AAC reactions (Table 2). If the basic nature of TBTA is the primary contributor to its acceleratory ability, TEA would also perform well. However, in most of the reactions, TEA performs only marginally better than the ligand-free reactions.

Consistently, ligand **6** (DTEA) outperforms TBTA in the AAC reactions in Table 2, in particular in reactions that involve an aromatic azide (Table 2, entry 3). The acceleratory effect of DTEA is tentatively attributed to its high basicity (4 tertiary amino groups) and its ability to bind copper(I/II) in a five-membered ring chelation similar to the coordination mode of TBTA.

The performance of DTEA was then evaluated in various protic and aprotic solvents by using the reaction between aliphatic azide 1-azidooctane and phenylacetylene. Complete conversions within 1 h were recorded in CH_3OH, *i*PrOH, *t*BuOH, as well as in aprotic toluene, acetonitrile, and THF (Table 3). In dichloromethane and HEPES buffer (pH 7.0), the reaction shows marginal conversion to product within 1 h but complete conversion within 24 h. Hexanes proved to be a poor solvent even over a 24 h reaction time. We attribute the decreased reactivity in HEPES, dichloromethane, and hexanes to substrate/solvent incompatibility rather than the impaired ligand efficiency, based on the fact that the ligand is soluble in all three solvents. The satisfactory solubility of ligand **6** in nonpolar solvents such as toluene and polar solvents such as water makes it advantageous for the $Cu(OAc)_2$-mediated AAC reactions in which solvent

Table 1. Substrate screening of the TBTA-assisted $Cu(OAc)_2$-accelerated AAC reaction.[a] Reaction times in min (conversion %) are listed.[b]



Entry					
1		A. 35 (100%) B. 90 (100%)	A. <5 (100%) B. 60 (100%)	A. 90 (100%) B. 300 (0%)	A. 60 (100%) B. 300 (40%)
2		A. <10 (100%) B. 30 (100%)	A. <10 (100%) B. 240 (100%)	A. 300 (100%) B. 300 (0%)	A. 300 (100%) B. 300 (0%)
3		A. <5 (100%) B. 300 (100%)	A. <5 (100%) B. <5 (100%)	A. 60 (100%) B. 300 (0%)	A. 60 (100%) B. 300 (0%)
4		A. 10 (100%) B. 20 (100%)	A. 60 (100%) B. 165 (100%)	A. 300 (71%) B. 300 (27%)	A. 30 (100%) B. 60 (100%)
5		A. <5 (100%) B. 10 (100%)	A. <5 (100%) B. <5 (100%)	A. 30 (100%) B. 300 (100%)	A. 30 (98%) B. 300 (100%)
6		A. 90 (100%) B. 300 (84%)	A. 15 (100%) B. 30 (100%)	A. 300 (91%) B. 300 (0%)	A. 300 (97%) B. 300 (0%)
7		A. <5 (100%) B. <5 (100%)	A. <5 (100%) B. <5 (100%)	A. 15 (100%) B. 10 (100%)	A. <5 (100%) B. <5 (100%)
8		A. 10 (100%) B. 45 (100%)	A. <5 (100%) B. <5 (100%)	A. 15 (100%) B. 300 (0%)	A. 15 (100%) B. 300 (100%)
9		A. 15 (100%) B. 60 (100%)	A. 300 (93%) B. 15 (100%)	A. 120 (100%) B. 300 (0%)	A. 120 (100%) B. 300 (0%)
10		A. 300 (24%) B. 300 (18%)	A. 300 (75%) B. 300 (0%)	A. 300 (0%) B. 300 (0%)	A. 300 (0%) B. 300 (0%)

[a] Reaction conditions: azide (0.2 mmol), alkyne (0.22 mmol), *t*BuOH (0.5 mL), $Cu(OAc)_2$ (25 μL, 0.4 M in H_2O), TBTA (5 mol% of azide). [b] Reaction times were determined by monitoring the disappearance of azide through TLC. The conversion values in the parentheses were determined based on ^{1}H NMR spectra of the crude products.

choice is highly dependent on the nature of the starting materials.

Mechanistic Investigations of the TBTA-Assisted $Cu(OAc)_2$-Accelerated AAC Reaction

Finn and co-workers conducted mechanistic studies on ligand-assisted CuAAC reactions.[11,18] The reaction between phenylacetylene and benzylazide in water shows a first-order dependence on the copper(I)/TBTA 1:1 complex, a zero-order dependence on azide, and a slight inhibitory effect from alkyne [Eq. (3), $x=-0.28$, $y=0$, $z=1.01$]:

$$\text{rate} = \frac{\text{d[triazole]}}{\text{d}t} = [\text{alkyne}]^x[\text{azide}]^y[\text{Cu/TBTA}]^z \qquad (3)$$

We recently developed an ^{1}H NMR spectroscopic assay to follow the progress of a homogenous $Cu(OAc)_2$-mediated AAC reaction that involved chelating azides in CD_3CN.[25] Herein, the ^{1}H NMR spectroscopic assay is applied to investigate the kinetic involvement of TBTA in $Cu(OAc)_2$-mediated AAC reactions that involve the nonchelating benzylazide in CD_3CN. Phenylacetylene and 1-ethynylcyclohexanol are selected as the alkyne substrates in two sets of measurements. The kinetic orders of individual components are listed in Table 4, along with results of Finn and co-workers for comparison.

The time course of a typical ^{1}H NMR spectroscopic experiment is separated into induction and reaction phases (e.g., see Figure 6). In the induction phase, no triazole product forms, while presumably the copper(I) catalytic species is generated. Triazole product emerges during the reaction phase. The initial rate of the reaction is considered to be the slope of the reaction phase in its steady state.

In the reaction between phenylacetylene and benzylazide, the kinetic order in phenylacetylene [x in Eq. (3)] is 1.3 (Figure 6), which is consistent with kinetically significant deprotonation of alkyne to form a copper acetylide intermediate.[26] At high alkyne concentrations, saturation kinetics appears to emerge, which indicates that the rate-determining step, or another kinetically significant step, follows the formation of copper acetylide. The induction period is progressively longer as [alkyne] decreases, thereby suggesting that the alkyne-requiring homocoupling reaction proceeds in the induction period.[27]

The kinetic order in benzylazide [y in Eq. (3)] is −0.3 (Figure 7), which indicates an inhibitory effect. Interestingly, the inhibitory effect was also observed in the induction period, which is prolonged with increasing [benzylazide]. This observation suggests that benzylazide is able to compete with phenylacetylene for copper(I/II) centers, which ultimately slows down the copper acetylide formation in both induction and reaction phases.

The putative 1:1 TBTA/$Cu(OAc)_2$ complex has a fractional kinetic order of 0.4 (Figure 8). As we speculated upon observing product inhibition in the preparation of the tris-triazole ligands, TBTA may form both active and inactive complexes with $Cu(OAc)_2$. The inactive species undercuts the contributions from both TBTA and copper(I/II). Due to the lack of a knowledge base of the coordination chemistry of TBTA and tris(triazolyl)-based ligands in general,[13] we do

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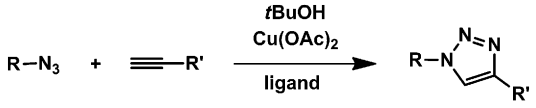
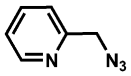
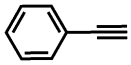
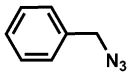
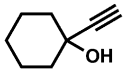
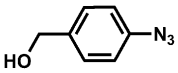
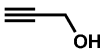
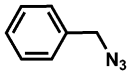
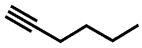
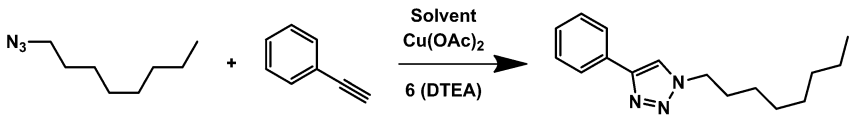
Table 2. Ligand effect in $Cu(OAc)_2$-accelerated AAC reactions.[a]



Entry	Azide	Alkyne	Ligand	t [min][b]	Conv. [%]
1			none	60	100
			TEA	20	100
			1 (TBTA)	5	100
			2 (TTMA)	25	94
			3 (THPTA)	20	100
			6 (DTEA)	2.5	100
			7	7	100
			8	25	100
2			none	60	100
			TEA	60	100
			1 (TBTA)	20	100
			2 (TTMA)	15	100
			3 (THPTA)	30	100
			6 (DTEA)	15	100
			7	20	100
			8	45	100
3			none	60	0
			TEA	60	0
			1 (TBTA)	20	100
			2 (TTMA)	30	100
			3 (THPTA)	60	100
			6 (DTEA)	<5	100
			7	20	100
			8	40	100
4			none	60	0
			TEA	60	34
			1 (TBTA)	60	74
			2 (TTMA)	60	87
			3 (THPTA)	60	0
			6 (DTEA)	60	100
			7	60	48
			8	60	35

[a] Reaction conditions: azide (0.2–0.22 mmol), alkyne (1.0–1.05 equiv), tBuOH (0.5 mL), $Cu(OAc)_2$ (25 μL, 0.4 M in H_2O), ligand (5 mol%). [b] Reaction times were determined by monitoring the disappearance of the azide through TLC. The conversion values were determined based on the ^{1}H NMR spectra of the crude products.

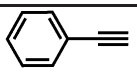
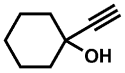
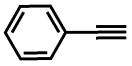
Table 3. Solvent effect on **6** (DTEA)-assisted $Cu(OAc)_2$-mediated AAC reaction.[a]



Entry	Solvent	Reaction time [h][b]	Conversion [%]
1	toluene	1	100
2	CH_2Cl_2	24	100
3	hexanes	24	<20
4	acetonitrile	1	100
5	methanol	1	100
6	t-butanol	1	100
7	HEPES (pH 7.0)	24	100
8	tetrahydrofuran	1	100
9	isopropanol	1	100

[a] Reaction conditions: 1-azidooctane (0.2–0.22 mmol), phenylacetylene (1.0–1.05 equiv), solvent (0.5 mL), $Cu(OAc)_2$ (25 μL, 0.4 M), ligand **6** (5 mol%) [b] Reaction times were determined by monitoring the disappearance of the azide through TLC. The conversion values were determined based on the ^{1}H NMR spectra of the crude products.

Table 4. Kinetic orders in various components of TBTA-assisted, $Cu(OAc)_2$-mediated AAC reactions (entries 1–6). The kinetic orders determined by Finn et al. using $CuSO_4$/sodium ascorbate combination are shown in entries 7–9.[11]

Entry	Alkyne	Solvent	[alkyne] [mM]	[BnN_3] [mM]	[Cu] [mM]	Varied component	Kinetic order
1		CD_3CN	8–20	16	0.8	alkyne	1.3
2	–	CD_3CN	16	8–18	0.8	azide	−0.3
3	–	CD_3CN	20	20	0.2–1	Cu/TBTA	0.4
4		CD_3CN	10–20	20	1	alkyne	1.5
5	–	CD_3CN	20	10–20	1	azide	≈0.5
6	–	CD_3CN	20	20	0.2–1	Cu/TBTA	1.3
7		H_2O	10–50	1	0.05	alkyne	−0.28
8	–	H_2O	1	10–50	0.05	azide	0
9	–	H_2O	1	1	0.02–0.25	Cu/TBTA	1.01

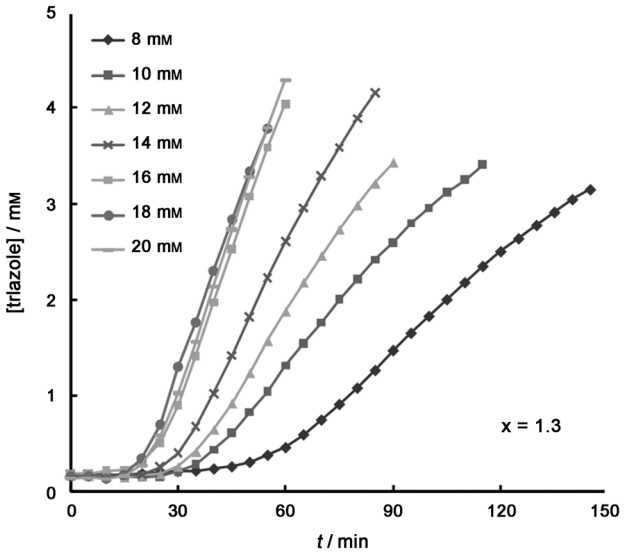


Figure 6. Dependence of reaction time course on [phenylacetylene] (8–20 mM). Conditions: [benzylazide] = 16 mM, [TBTA] = [$Cu(OAc)_2$] = 0.8 mM in CD_3CN, 300 K.

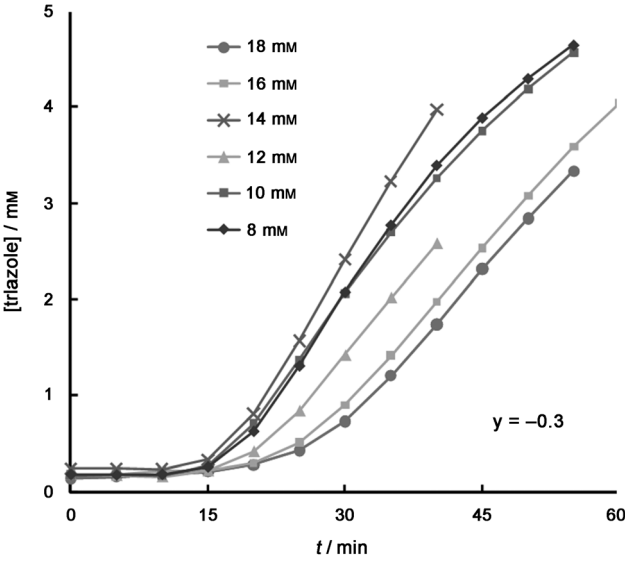


Figure 7. Dependence of reaction time course on [benzylazide] (8–18 mM). Conditions: [phenylacetylene] = 16 mM, [TBTA] = [$Cu(OAc)_2$] = 0.8 mM in CD_3CN, 300 K.

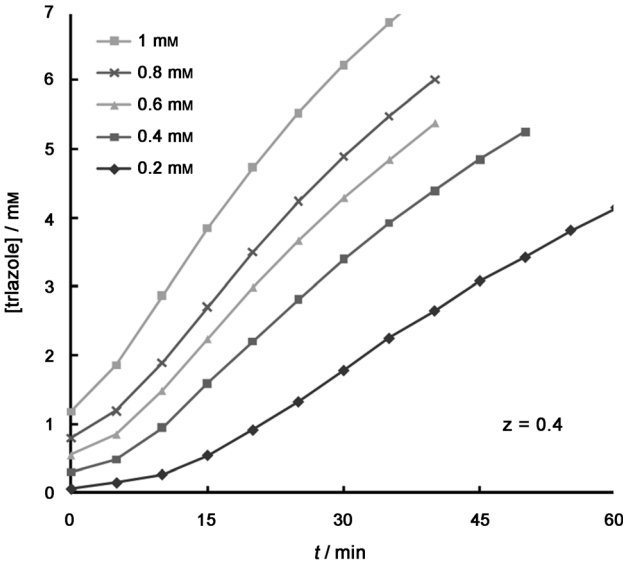


Figure 8. Dependence of reaction time course on [$Cu(OAc)_2$/TBTA] (0.2–1 mM). Conditions: [phenylacetylene] = 20 mM, [benzylazide] = 20 mM in CD_3CN, 300 K.

not attempt to offer a structural hypothesis on the remarkable acceleratory effect of TBTA on $Cu(OAc)_2$-mediated AAC reactions. On the other hand, based on the kinetic orders of copper(I/II)/TBTA complexes determined by Finn et al. and us, we incline to argue that TBTA-assisted CuAAC reactions may take a different pathway than the ligand-free version of the reaction, which has been shown to be second-order in copper.[25,28,29]

The kinetic orders of the reaction that involves 1-ethynylcyclohexanol reveal interesting substrate-dependent kinetic behaviors. Compared to phenylacetylene, 1-ethynylcyclohexanol carries a similar kinetic order of 1.5 (Figure 9). However, the induction periods are much shorter. This observation suggests that 1-ethynylcyclohexanol is a much better substrate than phenylacetylene in alkyne oxidative homocoupling reactions, probably due to its propensity to interact with copper(II).[30] For example, in the following hypothesized structure, the hydroxyl-directed π-complex formation aids the deprotonation of the ethynyl group and the subse-

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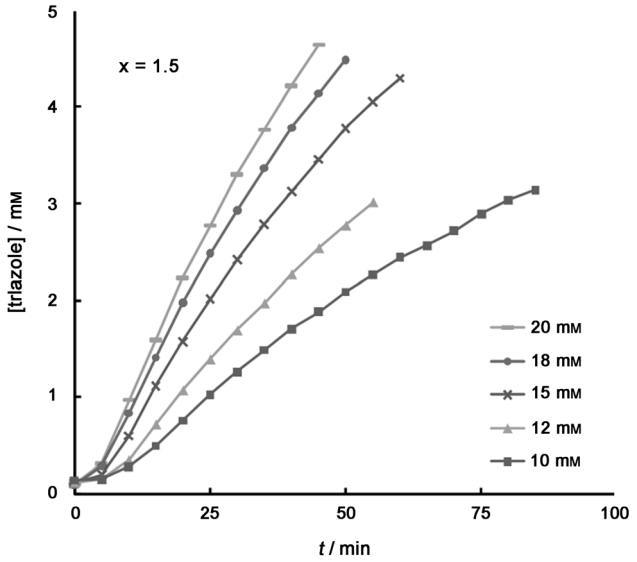
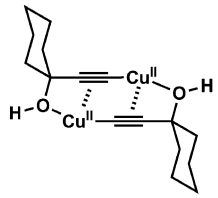


Figure 9. Dependence of reaction time course on [1-ethynylcyclohexanol] (10–20 mM). Conditions: [benzylazide] = 20 mM, [TBTA] = [$Cu(OAc)_2$] = 1 mM in CD_3CN, 300 K.



Scheme 5. Postulated dinuclear intermediate in the oxidative homocoupling of 1-ethynylcyclohexanol based on the report by Fedenok and Shvartsberg.[30]

quent formation of the dimeric copper(II) acetylide,[30] an intermediate in alkyne homocoupling reactions (Scheme 5).[8]

The strong 1-ethynylcyclohexanol/copper(I/II) interaction is further supported by the lack of azide dependence on the induction period (Figure 10), thereby suggesting that 1-ethynylcyclohexanol is able to overcome the inhibitory effect of benzylazide observed in the previous case that involves phenylacetylene. Consequently, the participation of benzylazide becomes kinetically significant, as a roughly 0.5 positive kinetic order was observed.

$Cu(OAc)_2$/TBTA complex shows a kinetic order of 1.3 (Figure 11), which is drastically larger than the previous case that involves phenylacetylene. Due to the high rate of ligand-free, $Cu(OAc)_2$-mediated AAC reaction that involves 1-ethynylcyclohexanol (Table 2, entry 2), the second order in copper of the ligand-free pathway, which is the background reaction, may be factored into the ligand-assisted kinetic order.[31]

Conclusion

Tris(triazolyl)-based ligands greatly facilitate $Cu(OAc)_2$-mediated AAC reactions that involve nonchelating azides. Based on this study, the known ligand TBTA, which has been applied extensively in assisting typical copper(I)-AAC reactions, and a new ligand DTEA are most effective in various $Cu(OAc)_2$-mediated AAC reactions. Both TBTA and DTEA can be conveniently synthesized by using the $Cu(OAc)_2$-mediated procedure. The three triazolyl groups form sequentially, with a product inhibition effect for the last triazole formation step. The kinetic-order determination reveals interesting substrate dependence of the reaction mechanism. An inhibitory effect of benzylazide can be overcome when an alkyne with a strong copper(I/II) affinity is used, such as 1-ethynylcyclohexanol. In addition to suggesting that competitive interactions with copper(I/II) by alkyne and azide lead to distinct mechanistic pathways of CuAAC reactions, this work provides evidence for the mechanistic synergy between CuAAC and alkyne oxidative homocoupling reac-

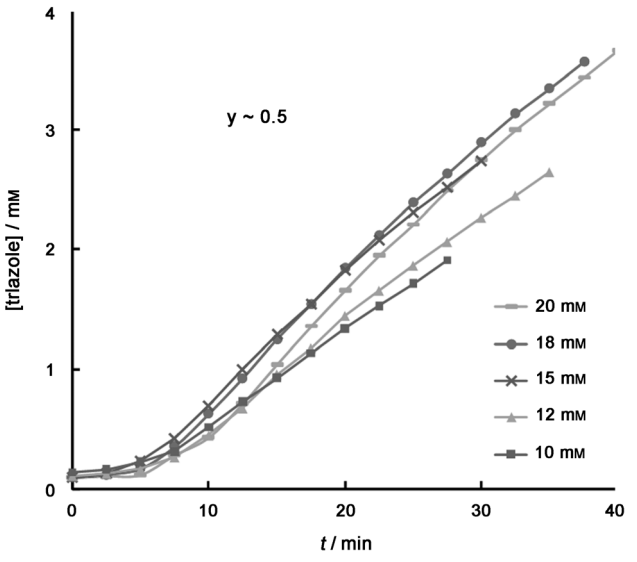


Figure 10. Dependence of reaction time course on [benzylazide] (10–20 mM). Conditions: [1-ethynylcyclohexanol] = 20 mM, [TBTA] = [$Cu(OAc)_2$] = 1 mM in CD_3CN, 300 K.

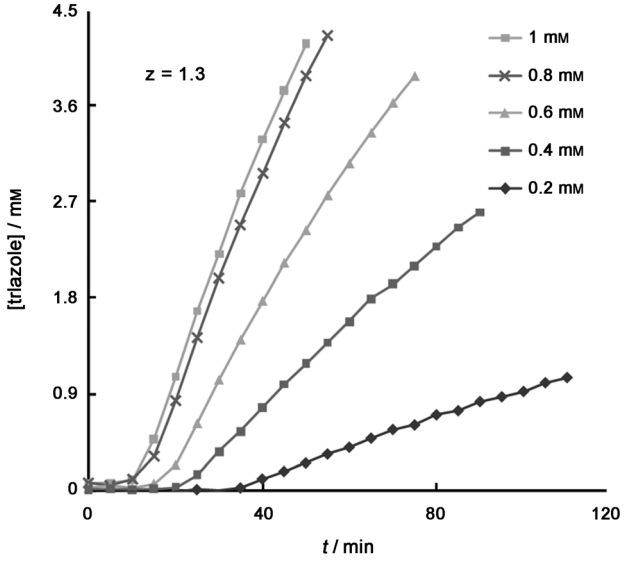


Figure 11. Dependence of reaction time course on [$Cu(OAc)_2$/TBTA] (0.2–1 mM). Conditions: [1-ethynylcyclohexanol] = 20 mM, [benzylazide] = 20 mM in CD_3CN, 300 K.

tions. The structural details of the involvement of TBTA and other polytriazole ligands in CuAAC reactions, however, are awaiting advances in the coordination chemistry of these ligands.

Experimental Section

General Procedure of $Cu(OAc)_2$-Mediated AAC Reactions

All azides and alkynes were used "as is" from the supplier or prepared from previously reported procedures.[32,9] Azide (0.80 M) and alkyne (0.82 M) stock solutions were prepared in *t*BuOH (>99.5%). An aqueous stock solution of $Cu(OAc)_2$ (0.4 M) was also prepared and used within 2 w. For reactions that involved an assisting ligand, 0.01 mmol (5 mol%) of the ligand was weighed into a reaction vial first. Azide (250 μL) and alkyne (250 μL) stock solutions were then added to the reaction vial along with an appropriately sized stir bar. No effort was made to exclude molecular oxygen. Upon injection of $Cu(OAc)_2$ stock solution (25 μL), the reactions were monitored with TLC. TLC was taken every 2.5 min for the first 15 min of reaction; between 15 min to 1 h, TLC was taken every 5 min. The frequency was reduced to every 30 min when the reaction ran over 1 h. The reaction mixture was diluted by ethyl acetate (2 mL) and was filtered through a pipette-sized column of alumina to produce the crude product. Chromatographic purification on an alumina column was carried out to afford the pure product, if needed.

^{1}H NMR Spectroscopic Kinetic Experiments

Stock solutions (2 mL each) of phenylacetylene (50 mM), benzylazide (50 mM), and the 1:1 complex of $Cu(OAc)_2$/TBTA (5 mM) were prepared fresh in CD_3CN for each set of data obtained. Aliquots of azide, alkyne, and CD_3CN were first combined in a small vial. The $Cu(OAc)_2$/TBTA catalyst was added last and the mixture was immediately transferred to an NMR spectroscopy tube and injected into the instrument. The total volume was 550 μL. Spectra were recorded at 300 K every 5 min. Data was collected on the same day for each experiment.

Acknowledgements

This work was generously supported by the National Science Foundation (CHE-0809201). We are indebted to Dr. Mioara Larion and Professor Brian Miller for guidance in using Pro Kineticist II software.

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[19] See more examples in: S. Diéz-González, *Catal. Sci. Technol.* **2011**, *1*, 166.
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[31] The apparent kinetic order of $Cu(OAc)_2$ includes the contributions of copper(I/II) to both induction and reaction phases. It should be noted that copper(I) may still be produced in the reaction phase, especially in relatively slow reactions. Therefore, we are at this point not in a position to propose a structural model to account for the kinetic orders of $Cu(OAc)_2$ in the ligand-assisted AAC reactions reported herein.
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