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Carboxylic Acid-Promoted Copper(I)-Catalyzed Azide−Alkyne Cycloaddition

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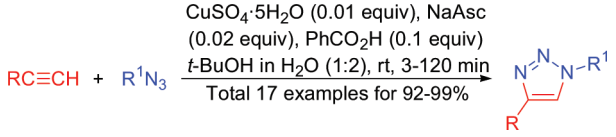
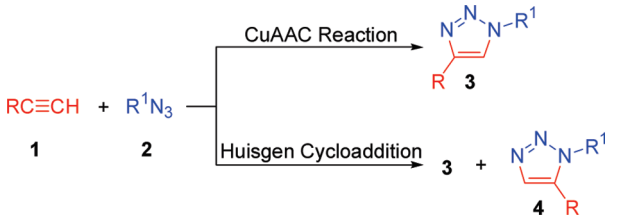


In this article, we proved that all three key steps in the catalytic cycle of CuAAC can proceed in the presence of carboxylic acids and the latter two steps can be promoted significantly by carboxylic acids. Benzoic acid showed the best promotion activity, and the acids with strong chelating ability to Cu(I) ion could not serve for this purpose. Thus, the first carboxylic acid-promoted highly efficient CuAAC was established.

The original Huisgen 1,3-dipolar cycloaddition[1] between alkyne (**1**) and azide (**2**) usually requires higher temperatures and provides a mixture of 1,4- (**3**) and 1,5-disubstituted 1,2,3-triazoles (**4**) (Scheme 1). However, these drawbacks can be overcome conveniently by using different Cu(I) catalysts. This Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC) was reported initially and independently by the groups of Sharpless[2] and Meldal[3] in 2002, which could proceed under mild conditions to give regioisomer **3** exclusively. Since then, CuAAC has been categorized as a "click reaction" and extensively studied and applied in the literature.[4−6]

SCHEME 1



Great attention has been paid to understand the mechanism of CuAAC in past years. A widely recognized three-key-step catalytic cycle was proposed by Sharpless in his first CuAAC article.[2] As shown in Figure 1, it starts from the formation of Cu(I) acetylide (**5**) and finishes by the protonation of the Cu−C bond in 5-Cu-substituted 1,2,3-triazole (**6**). Actually, the intermediates **5** and **6** (as coordination compounds) have been isolated and confirmed by ^{1}H NMR spectra.[7]

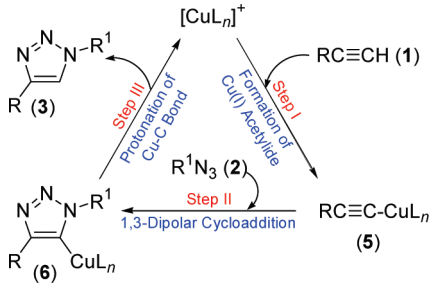


FIGURE 1

The investigation shows that the formation of Cu(I) acetylides (**5**) benefits from amine additives. For example, all practical procedures for the preparation of $[(PhC{\equiv}CCu)_2]_n$ (**5a**) proceed in ammonia solution.[8] In fact, an amine additive is essential for the preparation of $RC{\equiv}CCuL_n$ (**5**) in many published CuAAC procedures.[4] The amine additives accelerate the formation of **5** by two factors: (a) as a ligand, it could dissociate the stable clusters of Cu(I) salts to form the active Cu(I) species; (b) as a base, it could help to deprotonate the terminal acetylenes to form acetylides.

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(6) For selected references to CuAAC applications in 2010, see: (a) Sharma, P.; Moses, J. E. *Org. Lett.* **2010**, *12*, 2860. (b) Struthers, H.; Mindt, T. L.; Schibli, R. *Dalton Trans.* **2010**, *39*, 675. (c) Bakunov, S. A.; Bakunova, S. M.; Wenzler, T.; Ghebru, M.; Werbovetz, K. A.; Brun, R.; Tidwell, R. R. *J. Med. Chem.* **2010**, *53*, 254. (d) Carvalho, I.; Andrade, P.; Campo, V. L.; Guedes, P. M. M.; Sesti-Costa, R.; Silva, J. S.; Schenkman, S.; Dedola, S.; Hill, L.; Rejzek, M.; Nepogodiev, S. A.; Field, R. A. *Bioorg. Med. Chem.* **2010**, *18*, 2412. (e) Goldup, S. M.; Leigh, D. A.; McGonigal, P. R.; Ronaldson, V. E.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2010**, *132*, 315. (f) Ornelas, C.; Broichhagen, J.; Weck, M. *J. Am. Chem. Soc.* **2010**, *132*, 3923. (g) Pellico, D.; Gomez-Gallego, M.; Ramirez-Lopez, P.; Mancheno, M. J.; Sierra, M. A.; Torres, M. R. *Chem.—Eur. J.* **2010**, *16*, 1592. (h) Meyer, A.; Spinelli, N.; Dumy, P.; Vasseur, J.-J.; Morvan, F.; Defrancq, E. *J. Org. Chem.* **2010**, *75*, 3927.
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(8) For selected references, see: (a) Shi, W.; Luo, Y.; Luo, X.; Chao, L.; Zhang, H.; Wang, J.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 14713. (b) Woon, E. C. Y.; Dhami, A.; Mahon, M. F.; Threadgill, M. D. *Tetrahedron* **2006**, *62*, 4829. (c) Owsley, D. C.; Castro, C. E. *Org. Synth.* **1972**, *52*, 128.

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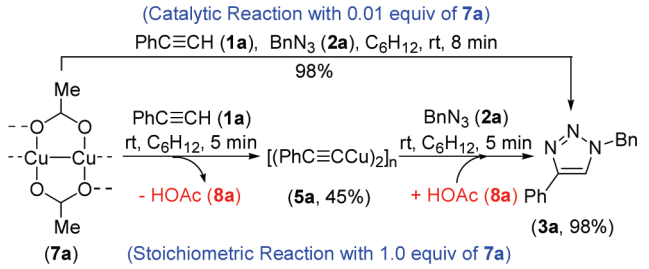
SCHEME 2



However, an amine additive is associated with two drawbacks: (a) it caused low efficiency in the protonation of the Cu−C bond of intermediate **6**; (b) it induced a byproduct by promoting the self-coupling of intermediate **5**. In fact, the low yields and byproduct have been reported by Sharpless in his first CuAAC article when Et_3N was used as an additive.[2] This may be the reason that the most common catalytic system to date for CuAAC is $CuSO_4$/NaAsc in neutral aqueous *t*-BuOH.

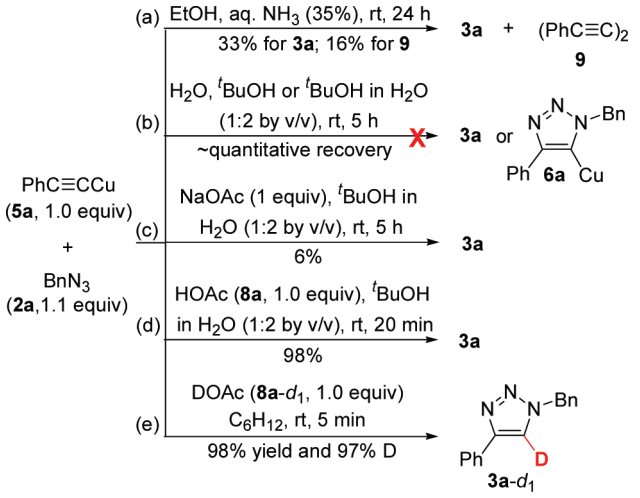
Recently, Straub reported that the protonation of the Cu−C bond of **6** was inefficient using H_2O or RC≡CH as a proton source, but it proceeded extremely fast (few minutes) in HOAc.[7b] This study clearly indicated that "step III" (see Figure 1) could not be improved even by using catalytic system $CuSO_4$/NaAsc in aqueous *t*-BuOH. It also strongly implied that a highly efficient CuAAC may be achieved if "step I" and "step II" could be influenced efficiently by HOAc.

However, there are no such reports in the literature where Cu(I) acetylides (**5**) can be prepared (step I) or carried out a 1,3-cycloaddition with azides (step II) in the presence of HOAc. Herein, we would like to report our recent efforts to understand the mechanistic cycle of CuAAC, by which the first carboxylic acid-promoted highly efficient CuAAC was established.

In the past years, two mechanistic concepts for CuAAC have been developed: (a) the catalytic CuAAC has a strict second-order dependence on Cu(I);[9] (b) the dinuclear or tetranuclear alkynyl-Cu(I) intermediate remarkably enhances the reactivity of CuAAC.[10] In our recent work, copper(I) acetate (**7a**) {a structurally well-defined dinuclear Cu(I) complex polymer $[(MeCO_2Cu)_2]_n$}-catalyzed highly efficient CuAAC was established based on these concepts.[5a] As shown in Scheme 2, with 0.01 equiv of **7a**, phenylethyne (**1a**) and benzyl azide (**2a**) carried out a CuAAC to give the desired product **3a** in 98% yield in 8 min. Further stoichiometric experiments provided two facts: (a) the catalyst **7a** reacted with **1a** to quickly yield $[(PhC{\equiv}CCu)_2]_n$ (**5a**), while an equimolar amount of HOAc (**8a**) was produced; (b) the "bare" **5a** (i.e., with no exogenous ligands) is not an active intermediate, but its cycloaddition with **2a** proceeded efficiently in the presence of HOAc (**8a**).

The results of Scheme 2 preliminarily indicate that all three key steps in the catalytic cycle of CuAAC can proceed in the presence of HOAc (**8a**). The formation of **5a** can be easily understood because **7a**, in fact, is a strong conjugate base of

SCHEME 3



the weak acid HOAc (**8a**). However, to understand the role of HOAc (**8a**) in the conversion of **5a** into **3a**, a group of control experiments were conducted (Scheme 3). (a) When the mixture of **5a** and **2a** was stirred for 24 h in the medium in which **5a** was prepared (a reference method),[8b] a new mixture of **3a** and the coupling product **9** was obtained. (b) When the mixture was stirred in H_2O, *t*-BuOH, or *t*-BuOH/H_2O for 5 h, **5a** was recovered in almost quantitative yield. (c) When the mixture was treated with a solution of NaOAc in *t*-BuOH/H_2O for 5 h, **3a** was obtained in 6% yield. (d) When the mixture was treated with HOAc (**8a**) in *t*-BuOH/H_2O for 20 min, **3a** was obtained in 98% yield. (e) When the mixture was treated with DOAc (**8a**-d_1) in cyclohexane for 5 min, the deuterium-labeled 5-D-1,2,3-triazole (**3a**-d_1, 97% D) was produced in 98% yield.

Although the expected intermediate **6a** or its analogues were not isolated, some conclusions may be drawn from Scheme 3. Experiments (a) and (b) proved that the cycloaddition of **5a** and **2a** was retarded in base or neutral medium. Experiment (c) proved that acetate itself could not accelerate the cycloaddition at all, even though it has been reported to enhance CuAAC (but it was not sufficiently investigated).[11] Experiment (d) proved that both cycloaddition and protonation of the Cu−C bond could be promoted by HOAc (**8a**). Experiment (e) not only showed that the cycloaddition can be promoted by DOAc (**8a**-d_1) but also implied that the intermediate **6a** or its analogues may exist because **3a**-d_1 was obtained exclusively.

Thus, HOAc (**8a**)-promoted CuAAC was studied further. As shown in Table 1, when **1a** and **2a** were treated by $CuSO_4$/NaAsc for 24 h under the reference conditions,[12] **3a** was obtained in 21% yield (entry 1) or in 99% yield with an amine ligand (entry 2). To our delight, when the same mixture of

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(10) (a) Straub, B. F. *Chem. Commun.* **2007**, 3868. (b) Ahlquist, M.; Fokin, V. V. *Organometallics* **2007**, *26*, 4389.
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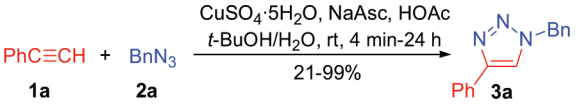
TABLE 1. HOAc (8a)-Promoted CuAAC between 1a and 2a[a]



entry	HOAc (**8a**) (equiv)	NaAsc (equiv)	solvent (mL)	time	yield of **3a** (%)[b]
1		0.04	3	24 h	21[c]
2	[d]	0.04	3	24 h	99[c]
3	0.5	0.04	3	40 min	96
4	0.4	0.04	3	20 min	97
5	0.3	0.04	3	35 min	97
6	0.4	0.02	3	21 min	98
7	0.4	0.02	1	6 min	98
8	0.2	0.02	1	4 min	98
9[e]		0.02	1	24 h	26
10[e]	0.2	0.02	1	5 min	97

[a]The mixture of **1a** (1 mmol), **2a** (1.05 mmol), $CuSO_4 \cdot 5H_2O$ (0.01 mmol), NaAsc, and HOAc (**8a**) in *t*-BuOH/H_2O (1:2 v/v) was stirred at room temperature. [b]Isolated yields. [c]The data were cited from ref 12. [d]0.1 equiv of 1-benzyl-4-aminomethyl-1,2,3-triazole was used as a ligand.[12] [e]$Cu(OAc)_2 \cdot H_2O$ (0.01 mmol) was used as a Cu(I) source.

TABLE 2. Carboxylic Acid-Promoted CuAAC between 1a and 2a[a]

entry	RCO_2H (**8**)	time (min)	yield of **3a** (%)[b]
1	$MeCO_2H$ (**8a**)	4.0	98
2	HCO_2H (**8b**)	3.5	97
3	$MeCH_2CH_2CO_2H$ (**8c**)	3.5	96
4	Me_2CHCO_2H (**8d**)	3.5	96
5	Me_3CCO_2H (**8e**)	3.0	98
6	$H_2C{=}CH(CH_2)_8CO_2H$ (**8f**)	4.0	95
7	CF_3CO_2H (**8g**)	30	94[c]
8	$C_6H_5CO_2H$ (**8h**)	1.0	98
9	$HO_2CCH_2CH_2CO_2H$ (**8i**)	1.5	96
10	1,3,5-$C_6H_3(CO_2H)_3$ (**8j**)	3.0	96
11	*trans*-$HO_2CCH{=}CHCO_2H$ (**8k**)	2.5	95
12	*cis*-$HO_2CCH{=}CHCO_2H$ (**8l**)	120	trace

[a]The mixture of **1a** (1 mmol), **2a** (1.05 mmol), $CuSO_4 \cdot 5H_2O$ (0.01 mmol), NaAsc (0.02 mmol), and RCO_2H (**8a**−**8l**, 0.2 mmol) in *t*-BuOH/H_2O (1:2 v/v, 1.0 mL) was stirred at room temperature. [b]Isolated yields. [c]0.02 equiv of CF_3CO_2H (**8g**) was used.

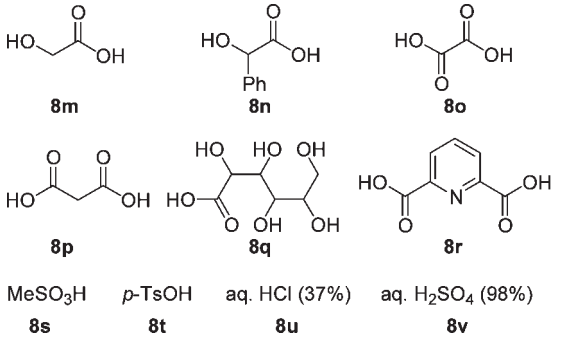


FIGURE 2. Selected chelate carboxylic acids and non-carboxylic acids.

entry 1 was treated with 0.5 equiv of **8a**, **3a** was obtained in 96% yield for 40 min (entry 3). By using 0.4 equiv of **8a**, the reaction finished in 20 min (entry 4), but a prolonged reaction time was needed when using 0.3 equiv of **8a** (entry 5). We interestingly observed that the reaction rate was significantly influenced by the ratio of HOAc, NaAsc, and solvent (entries 6−8). When their ratio was 0.2 (equiv):0.02 (equiv):1.0 (mL), the reaction finished within 4 min to give **3a** in 98% yield (entry 8). There was no advantage to replacing $CuSO_4 \cdot 5H_2O$ with $Cu(OAc)_2 \cdot H_2O$ (entries 9 and 10).

The investigation showed that all structurally well-defined Cu(I) carboxylates are dinuclear or polynuclear complexes.[14] Four of them have been proved to be excellent catalysts for CuAAC,[5a] such as $[(MeCO_2Cu)_2]_n$ (**7a**), $(PhCO_2Cu)_4$ (**7b**), $[(CF_3CO_2Cu)_4]_n$ (**7c**), and $[(t\text{-}BuCO_2Cu)_5]_n$ (**7d**). Therefore, the other carboxylic acids may be expected to have similar properties as HOAc (**8a**). As shown in Table 2, different carboxylic acids were tested, and the aliphatic acids **8a**−**8f** showed highly efficient promotion activity (entries 1−6). However, CF_3CO_2H (**8g**) could not afford the desired product at higher loading (0.2 equiv), but it gave comparable promotion activity at lower loading (0.02 equiv) (entry 7). To our surprise, $PhCO_2H$ (**8h**) gave the best result, by which **3a** was obtained in 98% yield within 1.0 min (entry 8). Succinic acid (**8i**) and benzene-1,3,5-tricarboxylic acid (**8j**) also gave excellent results because they have multicarboxylic acid groups (entries 9 and 10). Since *trans*-but-2-enedioic acid (**8k**) showed high promotion activity (entry 11) but its *cis*-isomer (**8l**) had no activity (entry 12), the carboxylic acids with strong chelating ability to Cu(I) ion may not serve for this purpose.

More experiments showed that all selected chelate carboxylic acids (**8m**−**8r** in Figure 2) did not have acceptable promotion activity for CuAAC. This result is in agreement with the phenomenon reported in the literature.[14] As was expected, non-carboxylic acids **8s**−**8v** were inert to CuAAC. For example, in the presence of **8s**−**8v**, no intermediate **5a** (characterized by a bright yellow color) was observed in catalytic CuAAC. When preformed **5a** was used as a substrate, it was decomposed by **8s**−**8v** within 5 min.

Interestingly, by using an equimolar mixture of **8v** and NaOAc (*in situ* formation of **8a**), **5a** was quickly produced and converted into product **3a** in 91% yield within 18 min. Since the inert[5a,b,9] polymer[15] **5a** could be activated by **8a** but not by **8v** or NaOAc alone, **8a** may play dual roles in the activation of **5a** as an acidic reagent and a bidentate ligand. As shown in Scheme 4, an active intermediate **5b** was proposed

(14) Xie, J.; Seto, C. T. *Bioorg. Med. Chem.* **2007**, *15*, 45.

(15) Dinuclear polymeric structure of $[(PhC{\equiv}CCu)_2]_n$ (**5a**): Chui, S. S. Y.; Ng, M. F. Y.; Che, C.-M. *Chem.—Eur. J.* **2005**, *11*, 1739.

SCHEME 4

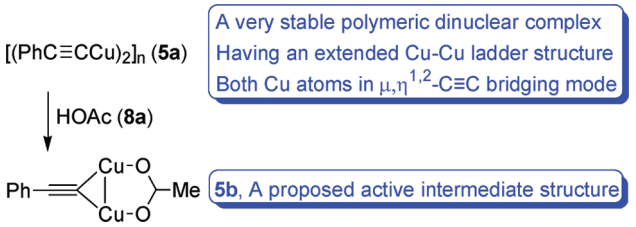


TABLE 3. $PhCO_2H$ (8h)-Promoted CuAAC between 1a and 2a[a]

entry	$PhCO_2H$ (equiv)	solvent (mL)	time (min)	yield of **3a** (%)[b]
1	0.2	2.0	1.0	97
2	0.1	2.0	4.0	98
3	0.05	2.0	20	98
4	0.02	2.0	40	98
5	0.02	0.2	3.0	98

[a]The mixture of **1a** (2 mmol), **2a** (2.1 mmol), $CuSO_4 \cdot 5H_2O$ (0.02 mmol), NaAsc (0.04 mmol), and $PhCO_2H$ (**8h**) in *t*-BuOH/H_2O (1:2 v/v) was stirred at room temperature. [b]Isolated yields.

(its structure remains unclear), which may be produced from the dissociation of **5a** by using **8a** as an acidic reagent followed by coordination with acetate by using **8a** as a bidentate ligand.

Thus, the combination of $CuSO_4$/NaAsc just served as a Cu(I) species producer. Once the Cu(I) species is produced *in situ*, it quickly coordinated with RCO_2H to generate a highly active catalyst $[(RCO_2Cu)_m]_n$. Thus, the method actually is still a Cu(I) carboxylate-catalyzed CuAAC reaction, but of greater advantage by its use of a cheap and stable Cu(II) source and alterable solvents.

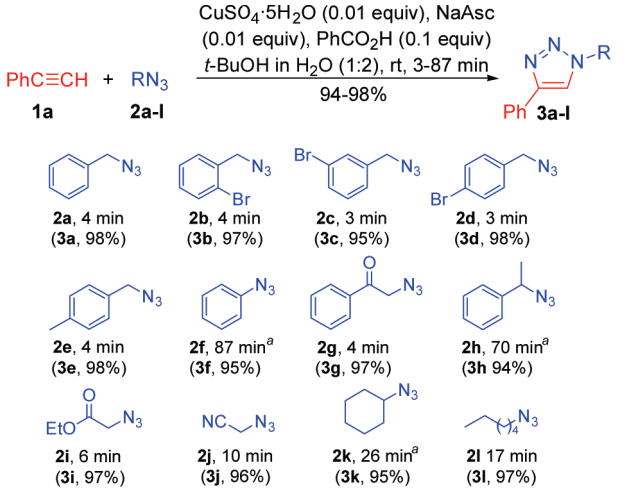
On the basis of the results in Table 2, $PhCO_2H$ (**8h**) was chosen as a promoter in practice. As shown in Table 3, it was so powerful that 0.1 equiv was good enough to give excellent results (entry 2). The results in entries 3−5 indicated that the reaction rate has been significantly accelerated by decreasing the amount of solvent. Finally, entry 2 was assigned as our standard conditions (rather than entry 1) for safety reasons because CuAAC is a highly exothermic reaction.

As shown in Scheme 5, excellent results were obtained between the reaction of phenylethyne (**1a**) and different azides (**2a**−**2e**, **2g**, **2i**, **2j**, **2l**) under the standard conditions. However, 0.2 equiv of $PhCO_2H$ (**8h**) was recommended to accelerate the reaction rate for the cases of substrates **2f**, **2h**, and **2k**.

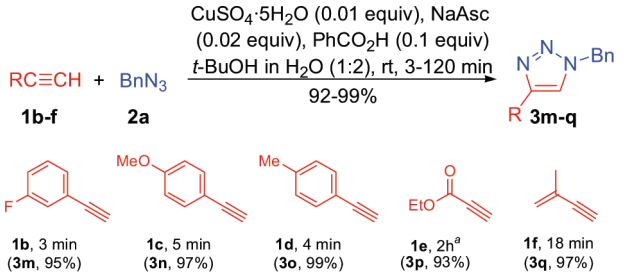
As shown in Scheme 6, the reactions between benzyl azides (**2a**) and different alkynes (**1b**−**1d** and **1f**) also gave excellent results. Under the standard conditions, more than 6 h was required for the substrate **1e**. However, the same conversion could be achieved within 2 h when 0.2 equiv of $PhCO_2H$ (**8h**) was used.

In conclusion, on the basis of the results of the control and the isotopic labeling experiments, we confirmed that all three key steps in the catalytic cycle of CuAAC can proceed in the presence of carboxylic acids. In fact, the later two key steps can be promoted significantly by carboxylic acids. Among the different types of carboxylic acids scanned, $PhCO_2H$ (**8h**) showed the best promotion activity. The carboxylic acids with strong chelating ability to Cu(I) ion and non-carboxylic acids could not serve for this purpose. To the best of our knowledge, this is the first carboxylic acid-promoted highly efficient CuAAC, and the dual functions (acid reagent and bidentate ligand) of carboxylic acids in CuAAC were discussed.

SCHEME 5



SCHEME 6



Experimental Section

Typical Benzoic Acid-Promoted CuAAC Procedure for the Preparation of 1-Benzyl-4-phenyl-1*H*-[1,2,3]trizole (3a). To a solution of $CuSO_4 \cdot 5H_2O$ (5.0 mg, 0.02 mmol), sodium ascorbate (7.9 mg, 0.04 mmol), and $PhCO_2H$ (24.4 mg, 0.2 mmol) in *t*-BuOH/H_2O (1:2 v/v, 2.0 mL) was added a mixture of phenylethyne (**1a**, 204 mg, 2 mmol) and benzyl azide (**2a**, 280 mg, 2.1 mmol) at room temperature. The resultant mixture was stirred continuously until the reaction system solidified completely (ca. 4 min). Then CH_2Cl_2 (20 mL) was added to dissolve the crude product. The organic layer was washed with H_2O and brine and dried over anhydrous Na_2SO_4. Removal of the solvent yielded a residue, which was purified by a short chromatography (silica gel, EtOAc/PE, 1:3) to give **3a** (461 mg, 98%) as an off-white solid.

A similar procedure was used in the preparation of products **3b**−**3q**.

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Note Added after ASAP Publication. Scheme 4 and Table 3 contained errors in the version published ASAP September 17, 2010; the correct version reposted September 22, 2010.

Supporting Information Available: Experiments, characterization, ^1H NMR and ^{13}C NMR spectra for products **3a**−**3q**, and ^1H NMR spectrum of **3a**-d_1. This material is available free of charge via the Internet at http://pubs.acs.org.