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Advanced Synthesis & Catalysis

General Cycloaddition Between a Trimethylsilyl-Capped Alkyne and an Azide Catalyzed by an N-Heterocyclic Carbene-Copper Complex and Pyridine-Biscarboxamide

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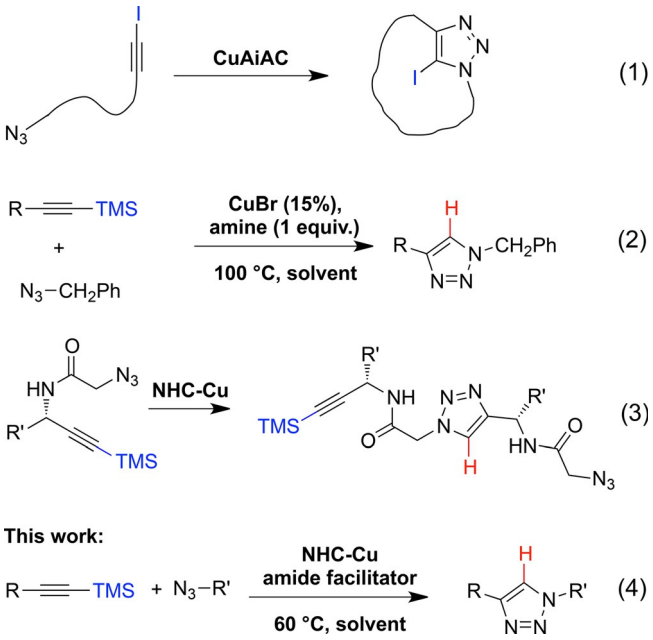
Abstract: With an externally provided catalytic amide facilitator and an N-heterocyclic carbene-copper (NHC-Cu) complex, the cycloaddition of an azide and a trimethylsilyl (TMS)-capped alkyne can proceed smoothly. This protocol can be applied to a variety of TMS-capped substrates, with electron-rich alkynes generally giving higher yields and nitroaromatic alkynes giving lower yields. For special applications of this protocol, a substrate containing both a terminal alkyne and a TMS-capped alkyne can sequentially react with different azides without isolation of intermediates; and a macrocyclic product can also be formed efficiently without the complication of polymer formation.

Keywords: catalysis; click chemistry; copper; CuAAC; cycloaddition; N-heterocyclic carbenes



Scheme 1. Copper-catalyzed cycloaddition reactions of azides and TMS-capped alkynes.

"Click chemistry",[1] a copper-catalyzed 1,3-dipolar cycloaddition reaction between an azide and a terminal alkyne (CuAAC), has extensive applications in medicinal chemistry,[2] materials science,[3] and chemical biology[4] due to the mild reaction conditions and excellent reaction specificity. In recent years, significant progress has been made in many aspects of CuAAC methodology to meet demands from diverse applications. For example, N-heterocyclic carbene (NHC) copper complexes were used as highly efficient catalysts for the reaction.[5] In order to efficiently form macrocylic cycloaddition products, copper-catalyzed azide iodoalkyne cycloaddition (CuAiAC) was developed [Eq. (1) in Scheme 1].[6] Direct CuAAC of TMS-capped alkyne was reported using CuBr, but the reaction was limited to the highly reactive benzyl azide [Eq. (2) in Scheme 1].[7] We previously showed that an NHC-Cu complex-catalyzed CuAAC can be conducted with TMS-capped alkynes when there is a nearby amide group that facilitates simultaneous removal of the TMS group during the cycloaddition process [Eq. (3) in Scheme 1].[8] However, the requirement of an amide moiety in the reaction substrate severely limits the utility of this transformation. Therefore, in this report, we investigate CuAAC for TMS-capped alkynes where the amide facilitator is provided externally as a catalyst so that the reaction can be generally applicable to a wide range of TMS-capped substrates [Eq. (4) in Scheme 1].

We began our investigation by screening several amide facilitators and NHC-Cu complexes (Figure 1). The screening uses TMS-capped phenylethyne and *n*-octyl azide as the substrates and was performed in 1:1

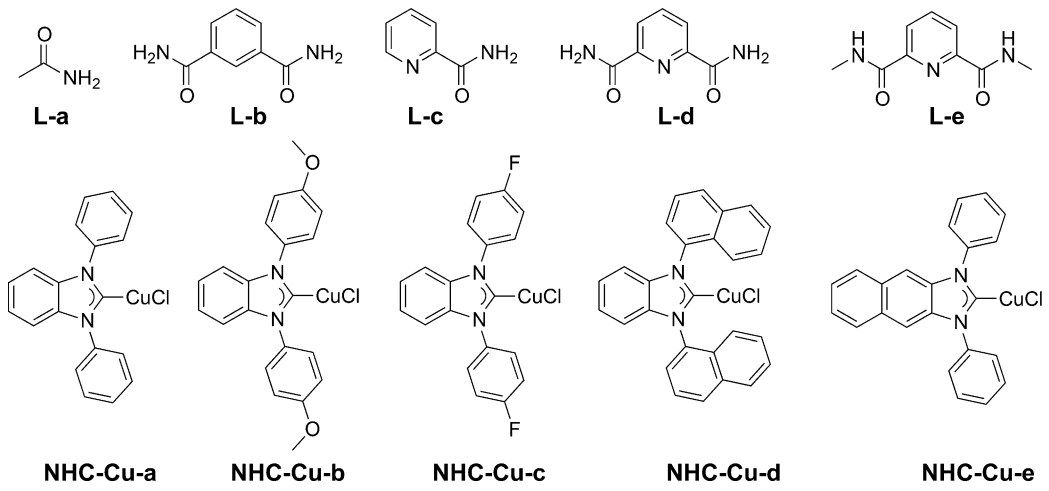


Figure 1. Structures of amide facilitators (**L**) and **NHC-Cu** complexes used in this work.

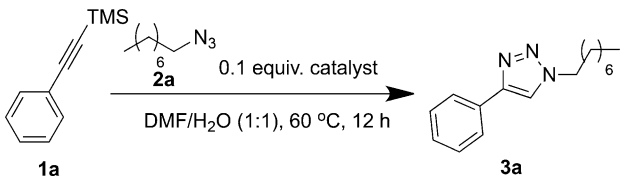
DMF: H_2O at 60 °C for 12 h. The choices of solvents, reaction temperature, and time were based on some preliminary studies (data not shown) covering a variety of mixed solvent systems (H_2O mixed with toluene, THF, *n*-BuOH, CH_3CN, DMF, or acetone), a temperature range from room temperature to 90 °C and a time range from 2–24 h.

The amide facilitators cover simple alkyl amides, phenyl bis-carboxamides, as well as pyridine mono- and bis-carboxamides specially chosen to allow potential coordination with the catalytic copper center so that one amide group can get close to the TMS group during the cycloaddition. Both the amide facilitator and the NHC-Cu (preformed in DMF with CuCl, NaOBu-*t*, and the corresponding NHC precursors in their imidazolium forms[9]) were used in catalytic amounts (0.1 equiv,). As shown in Table 1, CuCl alone or an NHC-Cu complex is not efficient to catalyze the desired reaction (entries 1 and 2 in Table 1). CuCl and the amide facilitator combinations (entries 3–7 in Table 1) can produce some desired product but the best combination (with **L-d**) still only gave 28% isolated yield. The combinations of NHC-Cu and **L-d** are consistently better performers (entries 8–12 in Table 1), and the best result was achieved with **NHC-Cu-e** (entry 12, 89%). For comparison, using the previously reported CuBr catalytic procedure,[7] only 23% yield was achieved for this model reaction (entry 13).

Using the best catalyst combination (**L-d** and **NHC-Cu-e**), we studied the substrate scope of this pyridine biscarboxamide and NHC-Cu promoted CuAAC protocol. The results are summarized in Table 2.

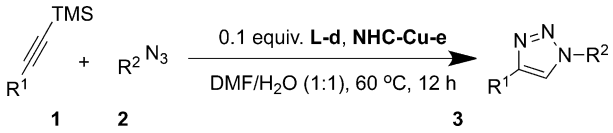
As shown in Table 2, for aromatic alkynes, phenylethynes with no substitution or with an electron-donating substitution on the phenyl ring (CH_3O) gave the best results with generally over 70% isolated yields (entries 1–5 in Table 2). Substitution on the phenyl ring with electron-withdrawing groups (Cl or CN, entries 6–11 in Table 2) could be well tolerated as well as a pyridylalkyne (entry 15), but with NO_2-substituted phenylalkynes the yields dropped to < 50% (entries 12–14). On the azide substrate side, the alkyl azides (*n*-octyl or benzyl) always performed better than the phenyl azide. This trend holds for TMS-capped alkylalkyne (entries 16–18 in Table 2), which performed similarly as phenyl- or Cl-phenylalkynes. From the 18 results in Table 2, we can conclude that our new CuAAC protocol using an external amide facilitator and an NHC-Cu complex can be generally

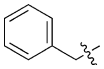
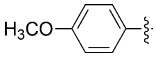
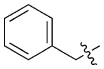
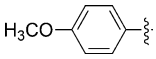
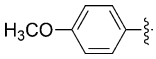
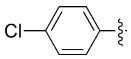
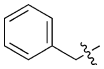
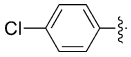
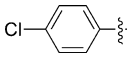
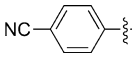
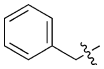
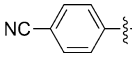
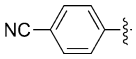
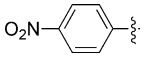
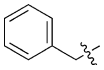
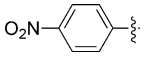
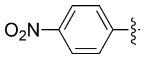
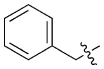
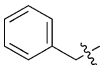
Table 1. Screening of amide facilitators and **NHC-Cu** complexes.



Entry	Catalyst	Isolated yield [%]
1	CuCl	trace
2	**NHC-Cu-e**	5
3	CuCl + **L-a**	trace
4	CuCl + **L-b**	trace
5	CuCl + **L-c**	5
6	CuCl + **L-d**	28
7	CuCl + **L-e**	8
8	**L-d** + **NHC-Cu-a**	32
9	**L-d** + **NHC-Cu-b**	30
10	**L-d** + **NHC-Cu-c**	36
11	**L-d** + **NHC-Cu-d**	42
12	**L-d** + **NHC-Cu-e**	89
13	CuBr (15%), Et_3N (1 equiv.), 100 °C in DMF	23%

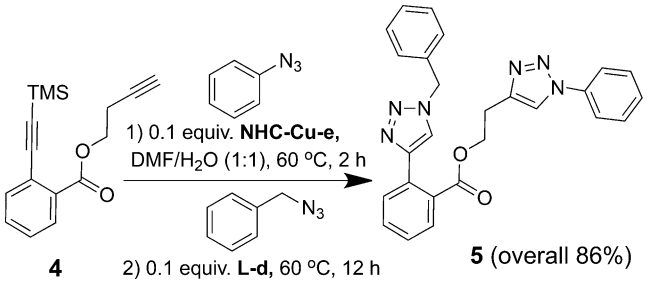
Table 2. Substrate scope of azide and TMS-capped alkyne cycloaddition.



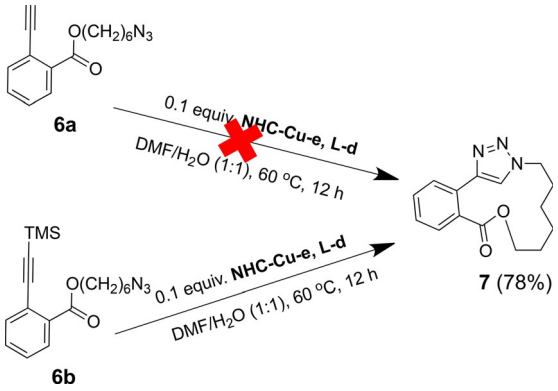
Entry	R^1	R^2	Product	Isolated yield	Yield using the reported CuBr procedure[b]
1			**3b**	88%[a]	90% (94/97%)[c]
2			**3c**	78%	28%
3			**3d**	91%	
4			**3e**	76%	
5		 n = 6	**3f**	90%	
6			**3g**	82%	6%
7			**3h**	59%	8%
8		 n = 6	**3i**	83%	36%
9			**3j**	75%	not detected
10			**3k**	68%	not detected
11		 n = 6	**3l**	76%	not detected
12			**3m**	35%	
13			**3n**	22%	
14		 n = 6	**3o**	49%	
15			**3p**	75%	
16	 n = 3		**3q**	83%[a]	55% (76/86%)[c]
17	 n = 3		**3r**	58%	not detected
18	 n = 3	 n = 6	**3s**	73%	not detected

[a] Reaction conducted at room temperature.
[b] Reaction conducted using the reported procedure with CuBr as the catalyst.[7]
[c] Yield as reported in the original paper.[7]

applicable to a variety of TMS-capped alkynes without the restriction of earlier examples that require an amide group in the substrate at a suitable position relative to the TMS group. For comparison, yields for selected reactions using the CuBr procedure are also included in the last column of Table 2. The entry 1 of



Scheme 2. Sequential CuAAC with a substrate containing both a terminal alkyne and a TMS-capped alkyne without isolation of intermediates.



Scheme 3. Synthesis of a macrocycle using an azido TMS-capped alkyne substrate.

Table 2 showed that the CuBr procedure can produce a high yield at 100 °C (90% in our hand *vs.* the reported 94/97% using different solvent systems), but our new procedure can achieve 88% at room temperature for the highly reactive benzyl azide. A similar result is achieved for entry 16 with the highly reactive benzyl azide. Overall, considering results for entries 1, 2, 6–11, and 16–18, our NHC-Cu plus amide facilitator procedure is much more suitable to a wide range of substrates than the high temperature CuBr procedure.

We next turned our attention to special applications of our new CuAAC protocol. One application is that if a reaction substrate contains both a TMS-capped alkyne and a terminal alkyne, one should be able to sequentially direct the cycloaddition with azides in the absence and presence of an amide facilitator. We demonstrate this utility in the reaction shown in Scheme 2. Compound **4** was first treated with phenyl azide in the presence of **NHC-Cu-e** to form a triazole with its terminal alkyne. Without intermediate isolation, to the reaction mixture was further added the amide facilitator **L-d** and benzyl azide to form the second triazole ring to give product **5** in 86% overall isolated yield. This process is clearly advantageous in that no deprotection step or intermediate isolation is necessary.

Another application of our new protocol is the synthesis of large macrocycles bridged by a triazole ring formed through CuAAC. Based on our previous study,[8] CuAAC with TMS-capped alkyne is less prone to polymerization when an azide group is present in the same substrate. To demonstrate this utility, we compared the cyclization reactions of two substrates. As shown in Scheme 3, the azido terminal alkyne substrate **6a** gave a polymer product with NHC-Cu catalysis, and no desired macrocyclic product **7** was isolatable. In contrast, the azido TMS-capped alkyne **6b** gave the desired macrocyclic product **7** in 78% isolated yield.

Based on the efficiencies of different amide facilitators (see Table 1), we believe that **L-d** is superior to others due to two factors: (i) the pyridine moiety and the carboxamides can help coordinate with the catalytic Cu center; and (ii) the presence of bis-carboxamide can ensure that at least one amide group is close to the TMS during cycloaddition. At this stage, it is not very clear why **L-d** is better than **L-e**. Nevertheless, we propose the following mechanism for the CuAAC of TMS-capped alkyne (Figure 2).

In summary, we have shown that CuAAC can be smoothly performed between an azide and a TMS-capped alkyne using catalytic amounts of an NHC-Cu complex and an amide facilitator (such as a pyridine biscarboxamide). The reaction protocol is generally compatible to a large number of substrate variants. Special applications of this protocol include sequential direction of CuAAC on a terminal alkyne and a TMS-capped alkyne; and the synthesis of a macrocycle bridged by a triazole ring to avoid polymerization

Plausible mechanism:

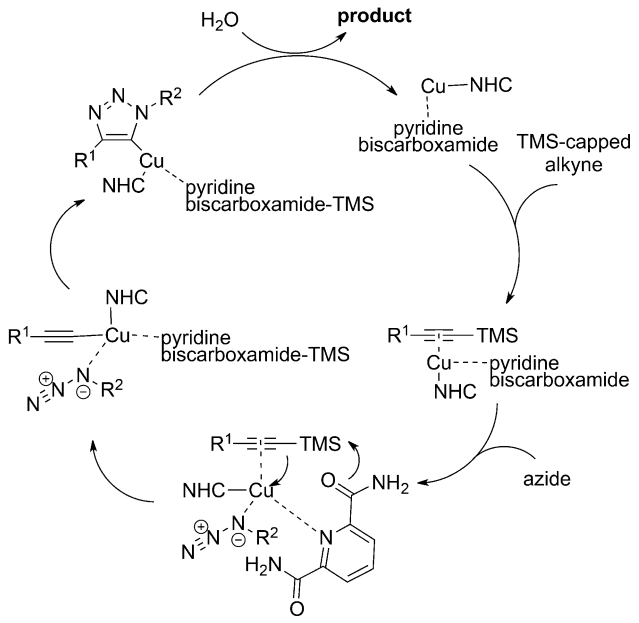


Figure 2. Proposed mechanism for CuAAC of TMS-capped alkynes catalyzed by **NHC-Cu** and pyridine biscarboxamide.

with uncapped terminal alkyne substrates. Our new procedure should complement existing CuAAC protocols in organic synthesis.

Experimental Section

General Procedure for the Synthesis of 3a–3s

NHC-e precusor (0.058 mmol) and potassium *tert*-butoxide (0.058 mmol) were stirred in DMF (2 mL) in a reaction vessel. After 0.5 h, a mixture of azide (0.58 mmol), TMS-capped alkyne (0.58 mmol), CuCl (0.058 mmol), pyridine-2,6-dicarboxamide (0.058 mmol) and water (2 mL) was added. The mixture was stirred at 60 °C for 12 h. After the completion of the reaction, the mixture was quenched by 30 mL water and then was extracted with ethyl acetate. The combined organic layer was loaded on a silica gel column and eluted with 10–20% ethyl acetate in hexane to afford the desired product **3a–3s**.

Acknowledgements

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