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Advanced Strategies for Efficient Macrocyclic Cu(I)-Catalyzed Cycloaddition of Azides

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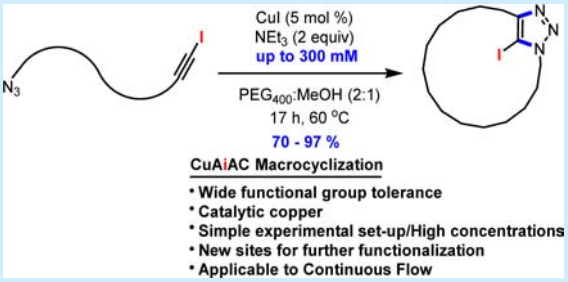
Supporting Information

ABSTRACT: An advanced strategy for efficient macrocyclic Cu(I)-catalyzed cycloaddition is described. The key features include employing azide−iodoalkyne cycloadditions (CuAiAC), low catalyst loadings, relatively high concentrations (30 mM → 300 mM), and application to continuous flow. The remarkably efficient new tool affords a variety of macrocyclic skeletons having either different alkyl, aryl, or amino acid spacers in high yields (70−97%). The macrocyclic CuAiAC process affords macrocycles having an iodotriazole moiety that can be further functionalized using standard Pd-catalyzed cross-couplings.



The copper-catalyzed azide−alkyne cycloaddition reaction[1] (CuAAC or commonly referred to as a "Click" reaction) has become an important synthetic strategy for the preparation of macrocycles.[2,3] Macrocyclic CuAAC processes have found application in medicinal chemistry for the preparation of macrocyclic carbohydrates,[4] peptides[5] and even rigidified drug-like macrocycles under continuous flow conditions.[6] Macrocyclic CuAAC has also found applications in materials science in the development of novel receptors, electronic materials, and molecular machines.[7]

Despite the wealth of applications, most macrocyclic CuAAC reactions still suffer from the slow rate of ring closing associated with conventional macrocyclization reactions (Figure 1). Consequently, long reaction times and high catalyst loadings (often superstoichiometric quantities of Cu), in combination with the use of high dilution and/or slow addition techniques to slow competing oligomerization, are necessary to obtain satisfactory macrocyclization.[8] The fact that these characteristic challenges remain prevalent in contemporary synthesis highlights the need for general reliable tools and/or strategies for efficient macrocyclization at high concentrations.[9] In an effort to develop such a process based upon "Click" strategies, the copper-catalyzed azide−iodoalkyne cycloaddition (CuAiAC) was identified as an ideal candidate for exploration as a macrocyclization technique. The CuAiAC process was recently reported as an efficient "Click" process, with several advantages over its CuAAC analog: (1) the iodoalkyne coupling partners are stable and readily accessible internal acetylenes[10] that exhibit reactivity typically greater than terminal alkynes in the cycloaddition process,[11,12] and (2) the formation of the product iodotriazoles also provides a convenient handle for further functionalization[13] and possibilities for diversity-oriented synthesis.[14] Despite the advantages, the CuAiAC reaction remains poorly explored (Figure 1), and only a single report of a macrocyclic variant employing a copper tubing reactor under continuous flow conditions has been reported.[15] Herein we report on an improved macrocyclic "Click" process through the development of an efficient macrocyclic Cu(I)-catalyzed azide−iodoalkyne cycloaddition process that can be performed at high concentrations using a phase separation strategy.

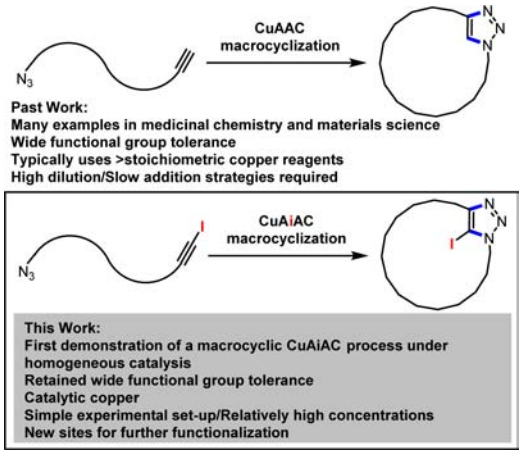


Figure 1. Macrocyclic azide−alkyne cycloaddition processes.

The development of a CuAiAC macrocyclization protocol that could be performed at high concentrations began with the design of an appropriate model substrate. An ideal acyclic precursor would be devoid of any structural motifs (heteroatoms, aryl groups) that could conformationally bias the molecule toward macrocyclization. Although the ring closing of such a precursor

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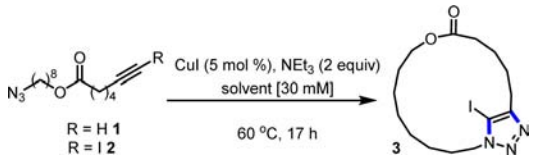
would be challenging, successful macrocyclization could be attributed solely to control of dilution effects.

Consequently, the azide−iodoalkyne **2** was selected for evaluation under phase separation conditions. The phase separation strategy has been previously reported to control dilution effects in macrocyclization reactions through the use of poly(ethylene) glycol (PEG) cosolvents.[16] Reaction media consisting of high ratios of PEG_{400}:MeOH formed aggregated mixtures, in which lipophilic PEG aggregates preferentially solubilize organic substrates. Slow diffusion out of a PEG aggregate into the MeOH cosolvent and subsequent cyclization are believed to mimic slow addition conditions, allowing for macrocyclization processes to be conducted at much higher concentrations while affording higher yields. Consequently, the macrocyclization of azide−iodoalkyne **2** was explored using catalytic systems previously developed for either CuAiAC intermolecular cycloaddition or CuAAC reactions in aqueous media. Initial investigations targeted a concentration of 30 mM using 1:1 mixtures of PEG_{400}:MeOH. First, catalyst systems using tridentate ligands were investigated, but both the $CuSO_4 \cdot 5H_2O/(BimC_4A)_3$/NaAsc[17] and $CuSO_4 \cdot 5H_2O$/TBTA[18]/NaAsc conditions failed to afford any of the desired 17-membered macrocycle **3** and none of the azide−iodoalkyne **2** was recovered.[19] When a catalyst system of CuI/NEt_3, previously exploited in intermolecular CuAiAC reactions,[17,18] was evaluated in a PEG_{400}:MeOH 1:1 solvent system, a 93% yield of the desired iodo-triazole macrocycle **3** was isolated (Table 1). The best yield

Table 1. Optimization of Macrocyclic CuAiAC Using a Phase Separation Strategy



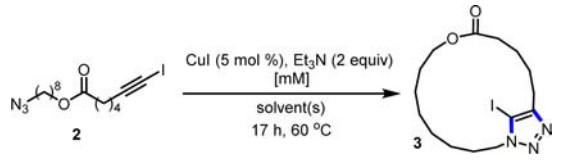
	conditions		
entry	solvent	yield **3** (%)[a]	recovered **2** (%)[a]
1	MeOH	23	poly
2	PEG_{400}	–	99[b]
3	PEG_{400}:MeOH 1:9	29	–
4	PEG_{400}:MeOH 1:2	60	–
5	PEG_{400}:MeOH 1:1	93	–
6	PEG_{400}:MeOH 2:1	97	–
7	PEG_{400}:MeOH 4:1	40	–[b]
8	PEG_{400}:MeOH 9:1	–	99[b]

[a]Yields following chromatography. [b]Product recovered was azide−alkyne **1**. No iodinated uncyclized products were observed.

(97% of **3**) was obtained at a PEG_{400}:MeOH 2:1 ratio.[20] Control reactions in the individual reaction solvents were examined. When azide−iodoalkyne **2** was treated with CuI/NEt_3 in MeOH, a 23% yield of macrocycle **3** was observed and extensive polymerization of the azide−iodoalkyne could be observed. When macrocyclization was attempted in PEG_{400}:MeOH 9:1 or just PEG_{400}, the deiodinated azide−alkyne **1** was isolated quantitatively.[21] The isolation of uncyclized azide−alkyne **1** at high PEG_{400}:MeOH ratios suggests that the reactivity of the catalyst system toward triazole formation was inhibited by the increasing concentrations of PEG_{400}, as is consistent with other reports of inhibition of transition metal catalysts by PEG solvent.[14b]

To demonstrate the ability of the PEG_{400}:MeOH solvent system to control dilution effects, the macrocyclization of azide−iodoalkyne **2** was first investigated at high dilution using the optimized catalyst system in MeOH (Table 2, entries 1 → 5).

Table 2. Concentration Effects of Macrocyclic CuAiAC Using Both Traditional High Dilution and Phase Separation Strategies



entry	solvent, concentration	yield **3** (%)[a]	yield **2** (%)[a]
1	MeOH, [0.2 mM]	–	99
2	MeOH, [0.2 mM][b]	43	22
3	MeOH, [1 mM]	–	99
4	MeOH, [1 mM][c]	56[d]	–
5	MeOH, [2 mM]	–	99
6	MeOH, [10 mM]	15[d]	15
7	MeOH, [30 mM]	23[d]	–
8	PEG_{400}:MeOH 2:1, [30 mM]	97	–
9	PEG_{400}:MeOH 2:1, [100 mM]	76	–
10	PEG_{400}:MeOH 2:1, [300 mM]	58	–

[a]Yields following chromatography. [b]Using CuI (20 mol %) and NEt_3 (8 equiv), 70 °C, 3 d. [c]Using CuI (2 equiv) and NEt_3 (80 equiv). [d]Formation of insoluble polymeric materials observed.

When the macrocyclization (**2** → **3**) was conducted at high dilution (0.2, 1, or 2 mM), little reaction was observed and the azide-iodoalkyne **2** was recovered quantitatively. In an effort to promote macrocyclization, a high dilution macrocyclization (0.2 mM) with higher catalyst loadings (20 mol %) and longer reaction times (3 d) was performed and afforded low yields and unconsumed azide−iodoalkyne (43% of **3**, 22% recovered **2**). Increased catalyst loadings (CuI (2 equiv)) could also coerce macrocyclization of **2** at 1 mM affording a 56% yield of triazole **3** and oligomerizing the remaining mass balance. It was hypothesized that increasing the concentration would help promote conversion, so the macrocyclization (**2** → **3**) was examined at higher concentrations in MeOH, but with a low catalyst loading (5 mol %) (entries 6 and 7). Macrocyclization at 10 mM afforded a 15% yield of **3** and 15% of azide−iodoalkyne **2**. At 30 mM, only a 23% yield of macrocycle **3** and extensive polymerization of **2** was observed. In contrast, at the identical concentration but using the PEG_{400}:MeOH (2:1) mixture, a 97% yield of macrocycle **3** was obtained. When employing the PEG_{400}:MeOH mixtures, the concentration could be further increased to 100 and 300 mM and good yields of macrocycle **3** were still obtained (a 58% yield of **3** at 300 mM). These results are in stark contrast to those obtained using traditional high dilution/slow addition techniques. Indeed, phase separation afforded superior yields at higher concentrations (1500× greater) with lower catalyst loadings (5−40× lower). The above results demonstrate that the phase separation allows for both greater concentrations and, consequently, lower catalyst loadings to be employed in macrocyclization reactions.

To demonstrate that the method can be used to prepare meaningful quantities of desired macrocycles, a gram-scale macrocyclization was performed using the optimized conditions with azide−iodoalkyne **2**. Upon scale-up to 1 mmol, the desired

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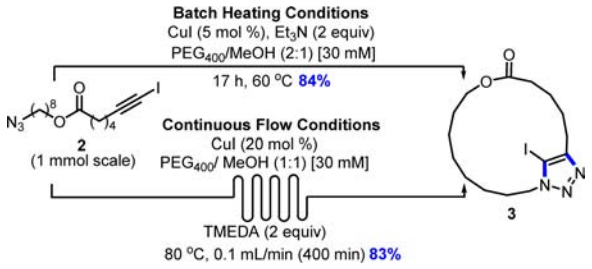
triazole macrocycle **3** was obtained in 84% yield (Scheme 1). To develop a more efficient demonstration of the ability to scale-up,

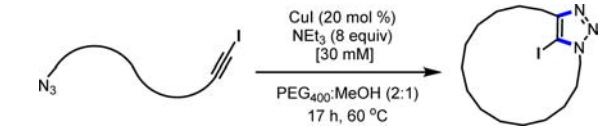
Scheme 1. Macrocyclic CuAiAC under Continuous Flow Conditions

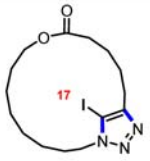
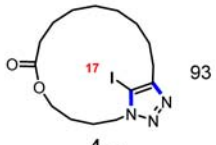
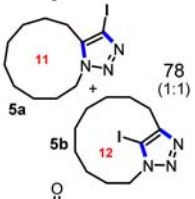
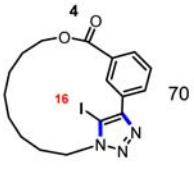
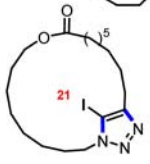
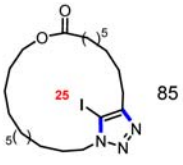
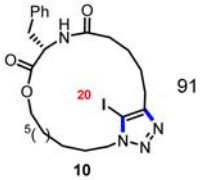
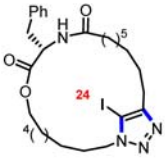
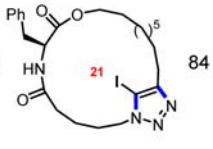
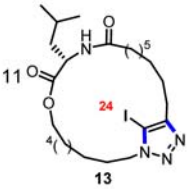
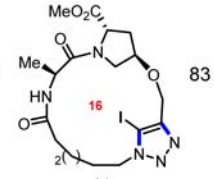


the "phase separation" strategy was adapted to a continuous flow protocol. Less than a handful of macrocyclizations under continuous flow conditions have been reported.[6,15,16c] Following optimization of temperature and flow rate, it was found that the azide−iodoalkyne **2** could be cyclized in good yield (up to 83%), in shorter reaction times than those from in batch (17 h vs ~6.6 h (400 min)). Importantly, the slightly higher temperatures involved required a change in the catalyst system. The use of a bidentate TMEDA ligand, in place of NEt_3, resulted in a reaction mixture which remained homogeneous throughout the reaction time.

With an optimized catalyst/solvent system in hand, a substrate scope for the macrocyclization was performed (Table 3).[22] The first acyclic precursors selected were purposely designed with flexible alkyl chains to evaluate the efficiency of the methodology with compounds having little structural or conformational bias toward cyclization. The 17-membered macrolactone **3** was obtained in 95% isolated yield, and the analogous 17-membered macrocycle **4** having different alkyl spacers was also obtained in excellent yield (93%) when subjected to the identical reaction conditions. In an attempt to prepare more challenging smaller ring sizes, the macrocyclic CuAiAC reaction to form the 12-membered ring **5b** was performed (entry 3). An excellent yield of 78% was observed; however, the macrocyclization had afforded a 1:1 ratio of two products: the desired 12-membered ring **5b** and the 11-membered ring **5a** which results from regioisomeric cycloaddition across the iodoalkyne.[23] Larger macrocycles such as the 21-membered **7** and the 25-membered **8** could also be prepared in good yields (87% and 85% respectively, entries 5 and 6). The 16-membered macrolactone **6** obtained from reaction with an aryl alkyne was isolated in 70% yield (entry 4). Once again, larger macrocycles bearing an aryl spacer, such as **9**, could be isolated in 75% yield using the optimized reaction conditions. The macrocyclic CuAiAC reaction was also applied to the cyclization of substrates having more complex structures including the presence of heteroatoms and chiral centers (Table 3, entries 8 → 12). Macrocycles having an embedded phenylalanine residue with different alkyl spacers were prepared in good yields; the 20-membered iodo-triazole macrocycle **10** was isolated in 91% yield. The size of the macrocycle could be expanded while maintaining good yields as the slightly larger 24-membered analog **11** was obtained in 83% yield. Also, the position of the azide and alkyne functionalities in the products could easily be reversed, as the 21-membered macrocycle **12** was isolated in 84% yield. Other amino acids could be incorporated, as the 24-membered isoleucine-derived macrocycle **13** was also cyclized at high concentration in high yield (86%).

Table 3. Substrate Scope of Macrocyclic CuAiAC Using a Phase Separation Strategy[a]



entry	macrocycle	yield (%)	entry	macrocycle	yield (%)
1		95	2		93
3		78 (1:1)	4		70
5		87	6		85
7		75	8		91
9		83	10		84
11		86	12		83

[a] Yields following chromatography. Ring size is indicated in red.

Again, to demonstrate the efficiency of the protocol on complex substrates, the synthesis of the peptidic macrocycle **17**[15] was performed. Macrocycle **17** had already been prepared by Bogdan and James during the synthesis of a library of peptidic macrocycles for drug discovery efforts in good yield (75%, [17 mM]). Bogdan and James also demonstrated further functionalization of the iodotriazole motif via Pd-catalysis. Under the optimized "phase separation" conditions, macrocycle **17** was obtained in 83% yield ([30 mM]).

In summary, a protocol for a macrocyclic Cu(I)-catalyzed azide−iodoalkyne cycloaddition (CuAiAC) is described. The CuAiAC is a remarkably efficient new tool for macrocyclization, affording high yields, at low catalyst loadings, at relatively high concentrations (30 mM → 300 mM) using a phase separation

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strategy. A variety of macrocyclic skeletons could be prepared having different alkyl, aryl, or amino acid building blocks. The macrocyclic CuAiAC is particularly attractive for industrial purposes, as (1) the process affords macrocycles having an iodotriazole moiety that is a convenient handle for use in diversity-oriented syntheses of macrocyclic libraries,[14] and (2) the ability to exploit continuous flow conditions allows for facile scale-up using nonvolatile/nontoxic PEG in place of large volumes of organic solvents. The macrocyclic CuAiAC reactions presented herein further suggest that phase separation is a viable technique for improving or developing novel macrocyclization processes. The effectiveness of the CuAiAC macrocyclization should be highly useful, given the prevalence of "click"-type strategies in fields such as material science and chemical biology.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) See Supporting Information for a full table of optimization for the macrocyclization. The TBTA and $(BimC4A)_3$ ligands were originally designed to promote triazole formation from terminal alkynes. See ref 17.

(20) Critical aggregation concentration (CAC) = 28% PEG_{400}:MeOH. The surface tension measurements can be used as a predictive tool to identify ratios of PEG:solvent that will be optimal for controlling dilution effects. For a graphic displaying the surface tension of the PEG_{400}:MeOH mixtures and yields of the macrocyclization, see the Supporting Information. For more information on the predictive use of the surface tension diagrams, see: Bédard, A.-C.; Collins, S. K. *Chem.—Eur. J.* **2012**, *19*, 2108.

(21) The mechanism for the formation of the deiodinated product is not understood at this time.

(22) Typically, macrocyclization reactions can be run at catalyst loadings of 5 mol %. In several cases, small amounts of unreacted starting material were difficult to separate from the desired macrocycle by simple silica gel chromatography. In these cases, the catalyst loading was increased to help promote complete conversion and facilitate purification.

(23) The lack of regioisomeric control in forming **11** and **12** is not understood at the current time. Changes in regiocontrol were not observed in strained macrocycles formed via CuAAC (see ref 6). It is possible that the lack of a Cu-acetylide intermediate may allow for changes in regiocontrol in macrocyclic CuAiAC reactions.