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CuAAC Macrocyclization: High Intramolecular Selectivity through the Use of Copper—Tris(triazole) Ligand Complexes

Gagan Chouhan and Keith James*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92014, United States

kjames@scripps.edu

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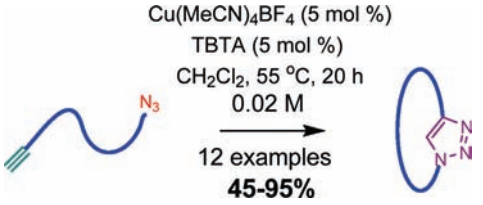
ABSTRACT



A range of multivalent heteroaryl ligands, copper sources, and solvent systems have been investigated for use in CuAAC-mediated macrocyclization reactions. These studies have revealed the key factors governing selectivity for macrocyclization versus dimerization and identified a simple but specific set of reaction conditions capable of efficiently generating a diverse series of drug-like macrocycles at modest dilution in up to 95% yield.

The design of macrocycles with drug-like structures and properties is an area of growing interest.[1] Consequently, there is a need for efficient macrocyclization methodologies that are capable of generating drug-like structures at reasonable scale without having to resort to high dilution conditions. The copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has emerged as an especially valuable transformation,[2] which generates a useful heterocyclic product (a 1,4-substituted 1,2,3-triazole) and can be used to close macrocyclic rings.[3] However, CuAAC macrocyclizations are still limited by the requirement for high dilution conditions in order to avoid intermolecular reactions, which is nonideal from practical, solvent consumption, and reaction rate perspectives.

Recent approaches to address the issue of concentration-dependent intra- versus intermolecular reaction include the use of solid-supported copper catalysts[3b] and copper tube flow reactors,[4] both of which aim to exploit a pseudo-dilution effect associated with heterogeneous

(1) (a) Driggers, E. M.; Hale, S. P.; Jinbo Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608–624. (b) Marsault, E.; Peterson, M. L. *J. Med. Chem.* **2011**, *54*, 1961–2004. Madsen, C. M.; Clausen, M. H. *Eur. J. Org. Chem.* **2011**, DOI: 10.1002/ejoc.201001715.

(2) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (c) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7–17. (d) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. (e) Lahann, J. *Click Chemistry for Biotechnology and Materials Science*; Wiley & Sons: New York, 2009. (f) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015.

(3) For recent selected examples of peptidic and nonpeptidic macrocycle synthesis via CuAAC reactions, see: (a) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674–1689 and references therein. (b) Haridas, V.; Lal, K.; Sharma, Y. K.; Upreti, S. *Org. Lett.* **2008**, *10*, 1645–1647. (c) Rowley Kelly, A.; Wei, J.; Kesavan, S.; Marie, J.-C.; Windmon, N.; Young, D. W.; Marcaurelle, L. A. *Org. Lett.* **2009**, *11*, 2257–2260. (d) Muthana, S.; Yu, H.; Cao, H.; Cheng, J.; Chen, X. *J. Org. Chem.* **2009**, *74*, 2928–2936. (e) Binauld, S.; Hawker, C. J.; Fleury, E.; Drockenmuller, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 6654–6658. (f) Latyshev, G. V.; Baranov, M. S.; Kazantsev, A. V.; Averin, A. D.; Lukashev, N. V.; Beletskaya, I. P. *Synthesis* **2009**, *15*, 2605–2615. (g) Day, J. E. H.; Sharp, S. Y.; Rowlands, M. G.; Aherne, W.; Workman, P.; Moody, C. J. *Chem.—Eur. J.* **2010**, *16*, 2758–2763. (h) Pirali, T.; Faccio, V.; Mossetti, R.; Grolla, A. A.; Di Micco, S.; Bifulco, G.; Genazzani, A. A.; Tron, G. C. *Mol. Diversity* **2010**, *14*, 109–121. (i) Holub, J. M.; Kirshenbaum, K. *Chem. Soc. Rev.* **2010**, *39*, 1325–1337. (j) Hu, T.-S.; Tannert, R.; Arndt, H.-D; Waldmann, H. *Chem. Commun.* **2007**, 3942–3944. (k) Berkel, S. S.; van Lee, B.; van der Delft, F. L.; van Rutjes, F. P. J. T. *Chem. Commun.* **2009**, 4272–4274. (l) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D.; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962–16976. (m) Nahrwold, M.; Bogner, T.; Eissler, S.; Verma, S.; Sewald, N. *Org. Lett.* **2010**, *12*, 1064–1067. (n) Jacobsen, Ø.; Maekawa, H.; Ge, N.-H.; Görbitz, C. H.; Rongved, P.; Ottersen, O. P.; Amiry-Moghaddam, M.; Klaveness, J. *J. Org. Chem.* **2011**, *76*, 1228–1238. (o) Pedersen, D. S.; Abell, A. *Eur. J. Org. Chem.* **2011**, *13*, 2399–2411. (p) Isidro-Llobeta, A.; Murilloa, T.; Belloa, P.; Cilibrizzia, A.; Hodgkinson, J. T.; Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, DOI: /10.1073/pnas.1015267108.

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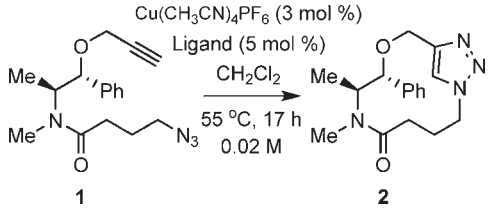
Table 1. Impact of Multivalent Heteroaryl Ligands on Yield and Product/Dimer Ratio for CuAAC Macrocyclizations



entry	ligand	yield (%)	**2**/dimer[a]
1	none	2.7	ND[b]
2	TBTA	88 (72)[c]	9.8:1 (7.5:1)[c]
3	TTTA	67	2.9:1
4	DBTA	57	3.5:1
5	TDTA	84	6.5:1
6	BBTA	82	6.0:1
7	$(Bim)_3$	23	ND[d]
8	BBTP	40	2.6:1
9	BTDE	57	2.9:1
10	BBMM	53	1.7:1[e]
11	BTMM	65	3.3:1[e]
12	PMDETA	43	1.2:1[e]

[a] Product-to-dimer ratio as determined by HPLC-MS analysis. [b] Reaction yielded primarily oligomers, plus 18% unreacted **1**. [c] Using μW at 110 °C for 1 h, 14% unreacted **1**. [d] Reaction yielded primarily oligomers, plus 49% unreacted **1**. [e] Using 5 mol % of $Cu(CH_3CN)_4BF_4$.

reaction conditions.[5] However, these methods still have limitations because they require either preparation and use of large amounts of catalyst resin or specialized flow equipment. Ideally, a methodology is required which uses small quantities of commercially available catalyst and which consistently produces a high ratio of intra- versus intermolecular reaction at practical concentrations (e.g., 0.02 M or above). This would facilitate both library production and scale-up.

In a recent study of CuAAC macrocyclizations under flow, using a copper tube reactor,[4] we noted a beneficial effect of tris(triazolyl) ligands such as tris((1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl)amine (TTTA) and tris((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine (TBTA) on the macrocycle-to-dimer ratios observed in these reactions. While the effect of these ligands on the rate of intermolecular CuAAC reactions has been highlighted previously,[6] and there have been sporadic reports on their use in macrocyclizations,[7] no systematic study of their effectiveness in facilitating CuAAC macrocyclizations has been reported. We have therefore investigated a range of multivalent heteroaryl ligands, together with a variety of copper

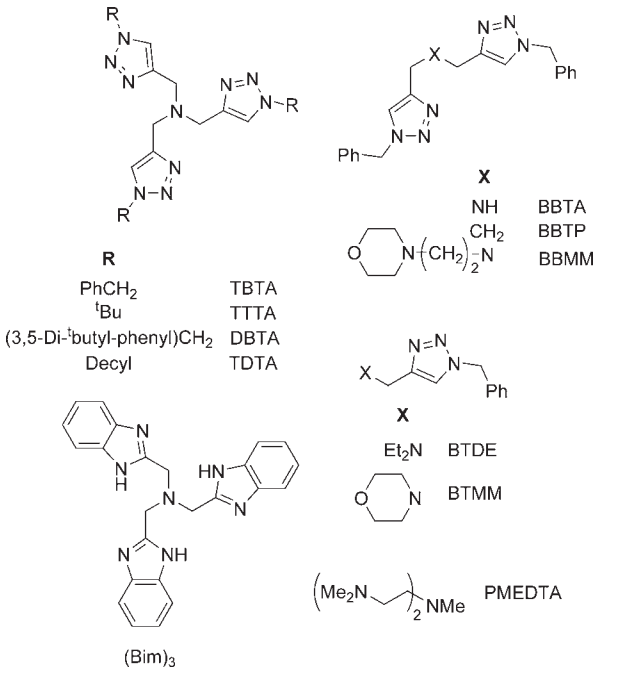


Figure 1. Ligands examined in the CuAAC macrocyclization.

sources and solvent systems, with the aim of finding an optimum set of conditions for effecting CuAAC-mediated macrocyclizations.[8a] We now report the outcome of these studies, which have revealed the key factors governing macrocyclization versus dimerization, as well as identifying a very specific but simple set of conditions capable of efficiently generating a diverse series of drug-like macrocycles at modest dilution in useful yields.

Azido-alkyne **1**, prepared in two steps from ephedrine, had proven to be a useful substrate in an earlier study of CuAAC-mediated macrocyclizations in flow[4] and so was used in a screen of homogeneous reaction conditions using HPLC-MS analysis to determine product-to-dimer ratios and yields (where the area under the dimer peak was assumed to include both cyclic and acyclic dimers). An initial survey of multivalent ligands was undertaken using a standardized protocol of solvent, copper source, reaction time, and temperature. Results are summarized in Table 1 (see Supporting Information for a comprehensive summary of conditions explored). The structures of the ligands used are shown in Figure 1.

Reaction in the absence of ligand yielded primarily oligomeric products (Table 1, entry 1), whereas addition of the tris(triazole) ligand TBTA produced a high product-to-dimer ratio and a high isolated yield of macrocycle (Table 1, entry 2), superior to those achieved with the more hindered ligands TTTA[6a] and DBTA or flexible alkyl-chain-substituted TDTA (Table 1, entries 3–5).[8b]

(4) Bogdan, A. R.; James, K. *Chem.—Eur. J.* **2010**, *16*, 14506–14512.
(5) Gonthier, E.; Breinbrauer, E. R. *Mol. Diversity* **2005**, *9*, 51–62.
(6) (a) Hein, J. E.; Krasnova, L. E.; Iwasaki, M.; Fokin, V. V. *Org. Synth.* **2011**, *88*, 238–246. (b) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302–1315. (c) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853–2855.
(7) Beierle, J. M.; Horne, W. S.; van Maarseveen, J. H.; Waser, B.; Reubi, J. C.; Ghadiri, M. G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4725–4729.
(8) (a) For review on various copper complexes and ligands used in CuAAC reactions, see: Díez-González, S. *Catal. Sci. Technol.* 2011, DOI: 10.1039/c0cy00064g. (b) For review on various tripodal ligands, see: Blackman, A. G. *Polyhedron* **2005**, *24*, 1–39.

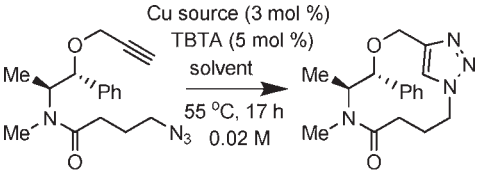
Bis((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine (BBTA),[9] a bidentate ligand, also achieved efficient macrocyclization, indicating that the third triazole moiety in the ligand probably does not play a crucial role in the macrocyclization mechanism (Table 1, entry 6). In contrast, ligands exhibiting stronger coordination to copper, such as the benzimidazole-based system $(Bim)_3$,[9] showed low conversion, low macrocycle yield, and primarily oligomers (Table 1, entry 7). A possible explanation for this observation is that the ability of the ligand to enable free coordination sites on the copper ion, via decomplexation of the weakly coordinated triazoles, might be a requirement for efficient macrocyclization.

To probe the role of the amine moiety in these ligands, the carba analogue of BBTA, bis(1-benzyl-1*H*-1,2,3-triazolyl)propane (BBTP), was evaluated. This resulted in a modest yield and product-to-dimer ratio (Table 1, entry 8), suggesting that the amine substituent in TBTA and BBTA does play a role, perhaps acting as a base to facilitate generation of a copper acetylide species. The monodentate ligand BTDE produced a modest yield and product-to-dimer ratio, suggesting that a ligand with at least two triazole moieties is required for optimal macrocyclization efficiency (Table 1, entry 9). Finally, either replacement of a triazole moiety with an amine (Table 1, entries 10 and 11) or use of a polydentate amine ligand (Table 1, entry 12) resulted in lower macrocycle-to-dimer ratios.

To further explore the importance of free coordination sites on the copper ion, we next examined the role of solvent and counterion. Halide counterions produced only modest product-to-dimer ratios and yields (Table 2, entries 1−3), consistent with coordination of the copper ion limiting macrocyclization efficiency. In contrast, use of a noncoordinating tetrafluoroborate counterion (Table 2, entry 4) resulted in a high product-to-dimer ratio and yield, comparable to the findings with the hexafluorophosphate counterion (Table 1, entry 2). Use of solvents likely to coordinate copper also reduced the product-to-dimer ratio, with acetonitrile having the most dramatic effect (Table 2, entries 5−7).

Finally, having identified an optimal set of choices for ligand, copper source, and solvent, we examined copper and substrate concentrations. Increasing copper concentration slightly, to achieve a 1:1 ratio of copper to ligand, resulted in a slightly higher product-to-dimer ratio and an excellent yield (Table 2, entry 8). Using these conditions, it was also possible to increase substrate concentration to 0.04 M and still achieve a very good yield of macrocycle (Table 2, entry 9). Our optimized conditions compare favorably to several recently reported resin-supported copper catalysts (for results with various resin-supported copper catalyst, see Supporting Information).[3b,10]

Table 2. Impact of Copper Source and Solvent on Yield and Product/Dimer Ratio for CuAAC Macrocyclizations[a]



1 **2**

entry	solvent	Cu source	yield (%)	**2**/dimer[a]
1	CH_2Cl_2	CuI	41	1.2:1
2	CH_2Cl_2	CuBr	51	1.3:1
3	CH_2Cl_2	CuCl	53	1.9:1
4	CH_2Cl_2	$Cu(CH_3CN)_4BF_4$	82	11.7:1
5	EtOH	$Cu(CH_3CN)_4PF_6$	77	4.9:1
6	dioxane	$Cu(CH_3CN)_4PF_6$	81	6.4:1
7	CH_3CN	$Cu(CH_3CN)_4PF_6$	<5	ND
8	CH_2Cl_2	$Cu(CH_3CN)_4BF_4$[b]	93	12.3:1
9	CH_2Cl_2	$Cu(CH_3CN)_4BF_4$[c]	78	9.8:1

[a] Product-to-dimer ratio as determined by HPLC-MS. [b] With 5 mol % of $Cu(CH_3CN)_4BF_4$. [c] With 0.04 M substrate concentration, 5 mol % of $Cu(CH_3CN)_4BF_4$.

Our results are consistent with several recent reports examining the sequence of steps in the CuAAC reaction mechanism and the nature of ligands used to accelerate this reaction. Thus, interaction of the noncoordinating copper salts with TBTA would be expected to yield a copper−ligand complex that can readily release a free coordination site for reaction with the azido-alkyne substrate. A recently reported X-ray structure of a $CuBF_4[CH_3CN]_4$/TBTA complex is essentially a symmetrical dimer of such a species, where the free coordination site has been occupied by a lone pair from the N-3 position of a triazole from a second TBTA molecule.[11] There is strong evidence from IR studies of intermolecular CuAAC reactions indicating that the first interaction with copper is via the alkyne rather than the azide, and so we would expect this to be the case with our azido-alkyne substrates.[12] Further decomplexation of the copper by one of the triazole ligands,[13] followed by recomplexation with either the pendant azido group or an azide from a second molecule, would then go on to yield the macrocycle or a dimeric product, respectively. It seems that, in comparison to the other ligands explored, the steric environment of the copper in the TBTA/tetrafluoroborate/alkyne complex preferentially favors reaction with the pendant azide rather than an azide from a second molecule.

(9) Presolski, S. I; Hong, V.; Cho, S.-H.; Finn, M. G. *J. Am. Chem. Soc.* **2010**, *132*, 14570–14576.

(10) (a) Chan, T. R.; Fokin, V. V. *QSAR Comb. Sci.* **2007**, *26*, 1274. (b) Lammens, M.; Skey, J.; Wallyn, S.; O'Reilly, R.; Prez, F. D. *Chem. Commun.* **2010**, 8719–8721.

(11) Donnelly, P. S.; Zanatta, S. D.; Zammit, S. C.; White, J. M.; Williams, S. J. *Chem. Commun.* **2008**, 2459–2461.

(12) (a) Sun, S.; Wu, P. *J. Phys. Chem. A* **2010**, *114*, 8331–8336. (b) Cantillo, D.; Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Org. Biomol. Chem.* **2011**, *9*, 2952–2958.

(13) For examples of decomplexation equilibria in tripodal copper complexes, see: (a) Eckenoff, W. T.; Pintauer, T. *Inorg. Chem.* **2010**, *49*, 10617–10626. (b) Tyeklar, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2677–2689.

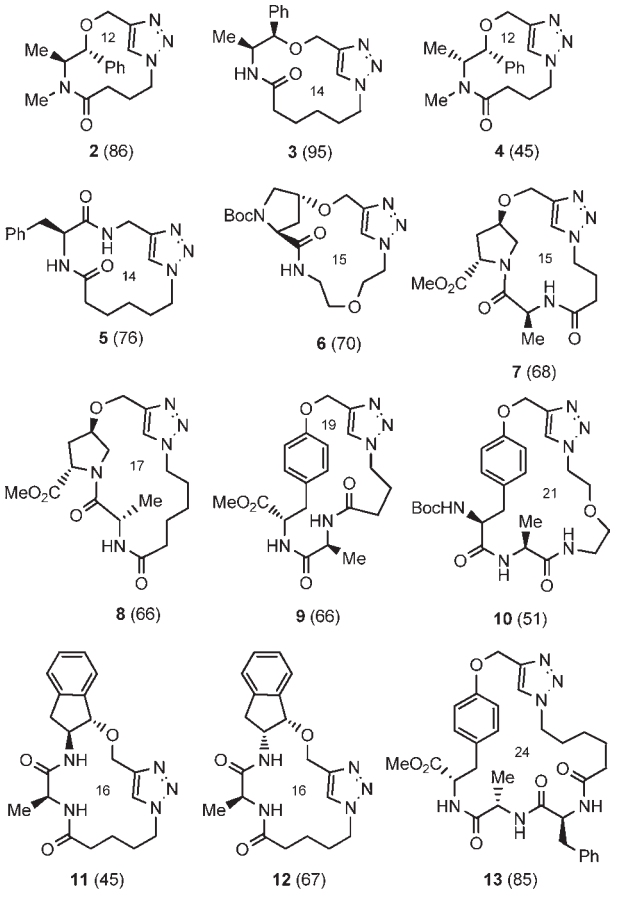


Figure 2. Substrate scope for CuAAC macrocyclization. Ring size is denoted by figure within the macrocyclic ring. Numbers in parentheses correspond to isolated yields after column chromatography. Macrocyclizations were conducted in CH_2Cl_2 at 55 °C, 0.02 M substrate concentration for 20 h, using TBTA (5 mol %) and $Cu(CH_3CN)_4BF_4$ (5 mol %).

Having developed an optimized macrocyclization protocol, we used this procedure to synthesize a small library of novel, drug-like macrocycles in mostly good to excellent yield, as illustrated in Figure 2. Macrocyclization substrates were available via short synthetic sequences from readily available homochiral starting materials (synthetic routes and full experimental procedures are available in Supporting Information). The macrocyclization procedure proved operationally very simple, and products could be isolated following solvent evaporation and column chromatography.

As illustrated in Figure 2, yields of macrocycles were generally high, with the norephedrine-derived system **3** being produced in 95% yield. Several systems were produced in less than 50% yield, which we believe results either from the stereochemical influence of substituent groups[14] (e.g., comparing yield of pseudoephedrine-derived macrocycle **4** versus the diastereomeric ephedrine-derived system **2**) or from the presence of a *trans*-ring junction (e.g., comparing the *trans*-aminoindanol-derived system **11** versus the *cis*-isomer **12**). Macrocycles of up to 24-membered rings were prepared in very good yield (Figure 2, example **13**), and on the basis of related studies, even larger rings are likely to be accessible. The macrocyclization conditions were compatible with the inclusion of multiple amino acid fragments, without any evidence of epimerization (examples **7**–**10** and **13**), although isolated yields were slightly lower in some cases because of challenges with solubility.

In conclusion, we have examined the parameters governing efficient macrocyclization via a CuAAC reaction and identified a simple set of optimized conditions which allow construction of novel macrocycles in up to 95% yield at only a modest level of dilution. We have exemplified the scope of this macrocyclization with a series of novel macrocycles which incorporate features typically found in biologically active agents. We expect this methodology to find use in the growing area of macrocycle-based drug design. We are currently investigating the use of this protocol for the macrocyclization of substrates supported on solid phase and will report our results in due course.

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

(14) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648–10649.