CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201002215

Efficient Access to New Chemical Space Through Flow—Construction of Druglike Macrocycles Through Copper-Surface-Catalyzed Azide–Alkyne Cycloaddition Reactions

Andrew R. Bogdan and Keith James*[a]

Abstract: A series of 12- to 22-membered macrocycles, with druglike functionality and properties, have been generated by using a simple and efficient copper-catalyzed azide–acetylene cycloaddition reaction, conducted in flow in high-temperature copper tubing, under environmentally friendly conditions. The triazole-containing macrocycles have been generated in up to 90% yield in a 5 min reaction, without resorting to the high-dilution conditions typical of macrocyclization reactions. This approach represents a very efficient method for constructing this important class of molecules, in terms of yield, concentration, and environmental considerations.

Keywords: click chemistry · flow chemistry · heterogeneous catalysis · macrocycles · synthetic methods

Introduction

Protein–protein interactions represent a critically important subset of molecular interactions, integral to both extra- and intracellular signaling pathways, which are poorly addressed by current small molecule drug-design strategies.[1] Macrocyclic systems offer a compelling approach to modulating these challenging molecular targets,[2] since their intrinsic conformational constraint and lower rotatable bond count offers the prospect of improved physicochemical,[3] pharmacological,[4] and pharmacokinetic[5] performance compared to their acyclic congeners. Although there are a number of examples of macrocyclic drugs derived from natural products,[2] totally synthetic macrocycles have received relatively little attention from drug designers, and represent only a tiny proportion of compound screening files.[6] In large measure, this is due to the challenge of efficient macrocycle synthesis. Thus, whilst the use of high-dilution conditions is the most common strategy employed in natural product synthesis to steer reactions towards macrocyclization, with concentrations often in the very low to submillimolar range,[7,8] this is impractical in a drug discovery setting, in which slow reaction times and high solvent quantity requirements are unacceptable from cost, capacity, and green chemistry perspectives.[9] A further consideration is that the functional group generated in the ring-closing reaction should be compatible with drug-property requirements (e.g., avoiding potentially metabolically vulnerable groups such as lactones, which feature commonly in natural product synthesis).[8]

Our objective has, therefore, been to devise macrocyclization methodologies that address these considerations and are applicable to drug discovery programs. We report, herein, a new approach for the efficient construction of a series of prototypical "druglike" macrocycles, without resorting to extremely high-dilution conditions, through the implementation of high temperature, copper-catalyzed cycloaddition chemistry in flow. To the best of our knowledge, this represents the first report of a macrocyclic closure under flow conditions.

Results and Discussion

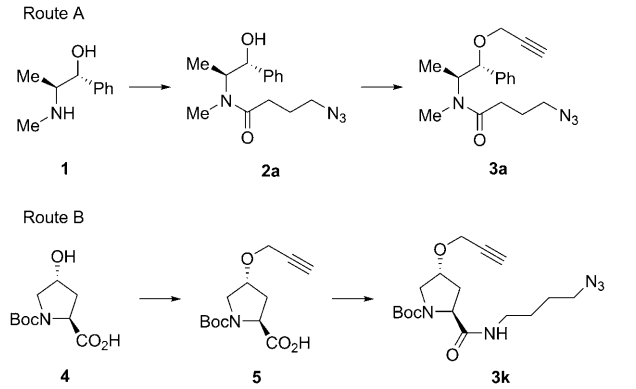
We were drawn to a flow methodology employing copper tubing as the reaction vessel for a number of reasons. Firstly, flow reactors have emerged as a powerful new technology for precisely controlling, and systematically exploring, key reaction parameters, such as reaction time, concentration, stoichiometry, and, in particular, temperature.[10] We,[11] and others,[12] have found previously that the macrocyclization

[a] A. R. Bogdan, K. James
Department of Chemistry, The Scripps Research Institute
10550 N. Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 8587847550
E-mail: kjames@scripps.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002215.

chemistry we selected, that is, the copper(I)-catalyzed azide–acetylene cycloaddition (CuAAC) reaction,[13] can be carried out under flow conditions to yield simple, linear heterocyclic products (1,2,3-triazoles) of the type typically found in drug molecules. In addition, the CuAAC reaction has recently found use in a number of macrocyclizations under nonflow conditions,[14] albeit with the aforementioned challenge of high dilution. Most importantly from our perspective, the generation of a reactive copper–acetylide species directly at or near the copper surface at high temperature might favor a rapid intramolecular reaction (to yield a macrocycle) before diffusion to encounter a second molecule (yielding a dimer).

Our aim was to construct a small library of macrocycles of varying ring size and functionality, available through short synthetic sequences (3–4 steps) from readily available, chiral, bifunctional starting materials, such as amino alcohols (**1**, Route A, Scheme 1) and hydroxy acids (**4**, Route B, Scheme 1).



Scheme 1. Synthesis of azidoalkyne macrocyclization precursors, starting from amino alcohols (**1**, Route A) and hydroxy acids (**4**, Route B).

Reactions were conducted in an Accendo Conjure flow reactor (Figure 1),[11] by using copper tubing (3 m length, 0.75 mm inner diameter) and 300–600 μL reaction segments. These discrete reaction segments were separated by perfluoromethyldecalin spacers, which prevent segment diffusion and reaction trailing. Such reactor systems are suitable for both reaction optimization and preparative-scale chemistry, and designed to withstand both elevated temperatures and pressures.

Azidoalkyne **3a** was used as a model system in the optimization of the flow macrocyclization. The intramolecular cycloaddition of **3a** to yield 12-membered macrocycle **6a** was performed under a variety of conditions, without the need for extraneous Cu^I salts in the reaction mixture, by using ethanol as the solvent (well above its boiling point), with a five-minute residence time (Table 1). Sufficient exposure to catalytic copper species is clearly achieved through interaction with the copper tubing alone. Elemental analysis data on the ethanol reaction mixture after it emerged from the copper tube indicated extremely low levels of copper present (< 5 ppm), suggesting that the catalytic copper species was either associated with the surface or could be desorbed from, and then readsorbed to, the surface along the course of the tube.[15] As expected, the ratio of product to dimer (determined by UV/Vis spectroscopy) was clearly sensitive to concentration (Table 1, entries 1–5); however, we chose to halt the dilution at 0.0167 M, a concentration significantly higher than most reported macrocyclizations.[8] The yield of **6a** was improved by incorporation of catalytic quantities of ligands that coordinate copper, presumably through complexation and activation of the copper species generated in situ (Table 1, entries 6–8). In particular, tris(triazolyl) catalysts[16] exhibited a marked effect on the product-to-dimer ratios and yields, with tris[(1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl]amine (TTTA) being the optimum ligand (Table 1, entry 8). Finally, the addition of *N*,*N*-diisopropylethylamine (DIPEA) further increased the amount of product, as well as the product-to-dimer ratio by ensuring complete recovery of the polar triazole products, which appeared to adhere to the reactor walls. Thus, under the optimized conditions, a 4.6:1 ratio of macrocycle to dimer was observed by UV/Vis spectroscopy, and macrocycle **6a** could be generated in 73% isolated yield (Table 1, entry 11). The structure of **6a** was confirmed by X-ray crystallography (Figure 2).

Given the spirited literature debate surrounding the value of flow chemistry,[17] we compared the reaction outcome achieved from our optimized flow protocol (Table 1, entry 11) to several other common reaction paradigms (Table 2). Thus, simply refluxing the ethanol reaction mixture together with stirred copper turnings (1 equiv) yielded

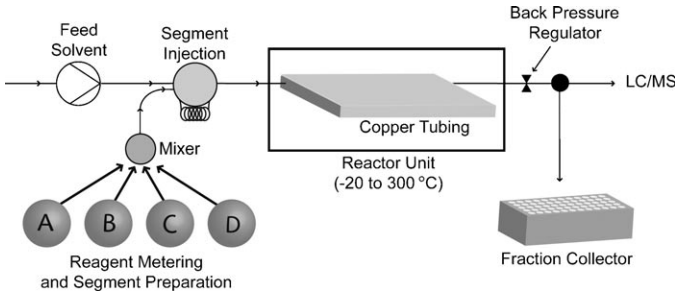


Figure 1. The flow reactor scheme. See the Supporting Information for more details.

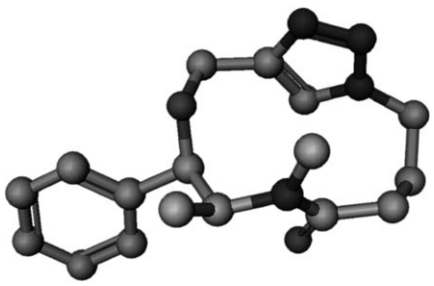
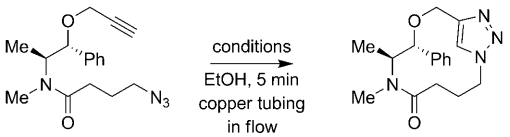


Figure 2. The X-ray crystal structure of macrocycle **6a**. Hydrogen atoms were omitted for clarity.

Table 1. Optimization of the flow macrocyclization reaction.[a]



3a 6a

	Additive	Concentration [M]	T [°C]	Product[b] [%]	**6a**:dimer[c]
1	–	0.1	100	<5	n.d.
2	–	0.1	150	13	0.34:1.0
3	–	0.05	150	13	0.37:1.0
4	–	0.0333	150	17	0.39:1.0
5	–	0.0167	150	24	0.44:1.0
6	TMP (10 mol%)	0.0167	150	31	0.71:1.0
7	TBTA (10 mol%)	0.0167	150	61	2.3:1.0
8	TTTA (10 mol%)	0.0167	150	72	2.6:1.0
9	TTTA (10 mol%) NH_3 (2.0 equiv)	0.0167	150	67	2.5:1.0
10	TTTA (10 mol%) TEA (2.0 equiv)	0.0167	150	77	3.8:1.0
11	TTTA (10 mol%) DIPEA (2.0 equiv)	0.0167	150	79 (73)[d]	4.6:1.0
12	DIPEA (2.0 equiv)	0.0167	150	21	0.34:1.0

[a] TMP = 3,4,7,8-tetramethyl-1,10-phenanthroline, TBTA = tris[(1-benzyl-1*H*-1,2,3-triazolyl)methyl]amine, TEA = triethylamine, n.d. = not determined. [b] Percent product as determined by HPLC–MS analysis. [c] Product-to-dimer ratio as determined by HPLC–MS analysis [d] Isolated yield after column chromatography.

Table 2. Comparison of flow and non-flow macrocyclization reactions.

	Reaction conditions[a]	Product[b] [%]	**6a**:dimer[c]
1	Cu turnings (1.0 equiv), reflux, 5 min	n.r.	–
2	Cu turnings (1.0 equiv), reflux, 90 min	<5	n.d.
3	CuI (0.2 equiv), reflux, 5 min	9	1.0:1.0
4	CuI (1.0 equiv), reflux, 5 min	20	1.1:1.0
5	CuI (1.0 equiv), 150°C, 5 min	52	1.5:1.0
6	Cu turnings (100 wt. equiv), 150°C, 5 min	17	1.1:1.0
7	Cu powder (100 wt. equiv), 150°C, 5 min	50	1.5:1.0
8	no copper additive, 150°C, 5 min, Hastelloy tubing, flow[d]	<5	n.d.
9	CuI (1.0 equiv), 150°C, 5 min, Hastelloy tubing, flow[d]	68	2.6:1.0
10	CuI (0.004 equiv), 150°C, 5 min, Hastelloy tubing, flow	35	n.d.

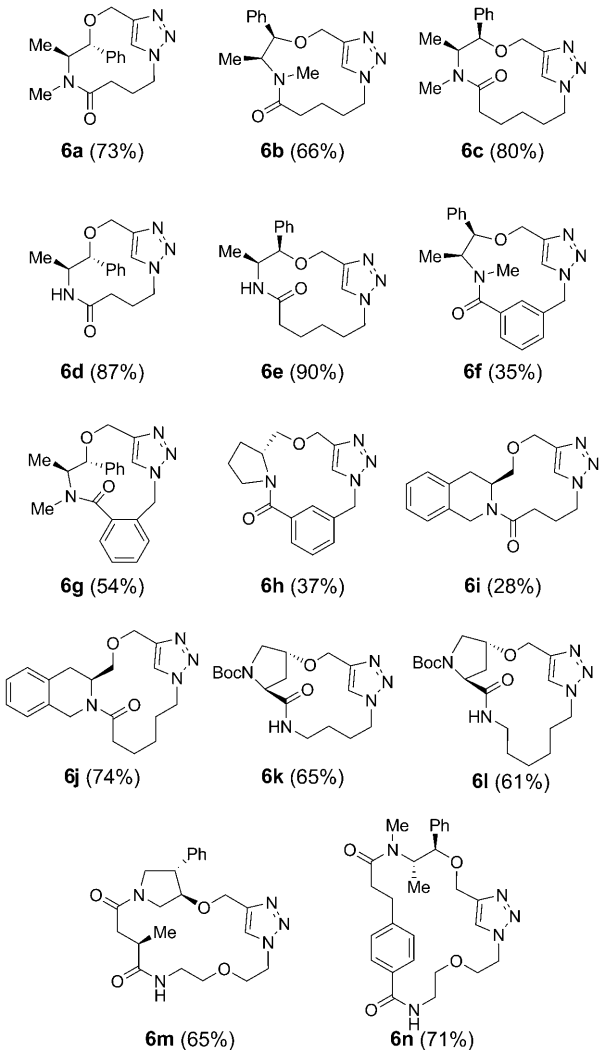
[a] [**3a**] = 0.0167 M, DIPEA (2.0 equiv), TTTA (10 mol%); n.r. = no reaction; n.d. = not determined. [b] Percent product as determined by HPLC–MS analysis. [c] Product-to-dimer ratio as determined by HPLC–MS analysis. [d] MeCN used to help dissolve the CuI. Reaction segments contained a 2:1 v/v ratio of EtOH to MeCN.

no detectable product after 5 min and only trace amounts of product after 90 min (Table 2, entries 1 and 2). Although much less environmentally appealing, we also examined the addition of soluble CuI (0.2 or 1 equiv), which resulted in a low yield of product and only a 1:1 ratio of macrocycle to dimer (Table 2, entries 3 and 4). In an effort to more closely replicate the flow protocol, this same reaction mixture was heated in a sealed tube at 150°C for 5 min by using an oil bath (chosen to enable precise timing of heating) in the presence of CuI (1.0 equiv), copper turnings (100 wt. equiv), or copper powder (100 wt. equiv), yielding 52, 17, and 50% product by UV/Vis spectroscopy, respectively, although with considerably lower product-to-dimer ratios (Table 2, entries 5–7).

Finally, the reaction was run in flow by using Hastelloy tubing (Table 2, entries 8–10). Without a copper source, the reaction gave <5% product. With soluble CuI (1.0 equiv), the reaction yielded 68% product by UV/Vis spectroscopy, but with a product-to-dimer ratio of only 2.6:1.0. With 0.004 equivalents of CuI, which was calculated to approximate the maximum amount of copper detected by elemental analysis in the reaction segments emerging from the copper reactor, the reaction was incomplete and yielded only 35% product by UV/Vis spectroscopy. In this final case, the product-to-dimer ratio was not determined due to the broad peak shape of the dimer giving inaccurate integrations when present in only small amounts. Again, these results emphasize the key role played by the copper tubing.

By using the optimized copper-tube flow protocol, we examined the macrocyclization of a range of azidoalkyne substrates based upon various chiral fragments, thereby generating a diverse collection of 12- to 22-membered macrocycles (Scheme 2). In all cases, the desired macrocycles were generated at the same moderate concentration (0.0167 M) and in modest to excellent yield.

Macrocycles **6a**, **b**, and **c** represent a homologous series of 12-, 13-, and 14-membered rings, respectively, all of which were generated in good yield. Macrocycles **6d** and **e**, which lack an *N*-methyl substituent and are thus less sterically congested, were formed in excellent yields of 87 and 90%, respectively. Macrocycles **6f–i**, generated in lower yields, represent much more strained systems by virtue of the additional conformational constraints resulting from the embedded aryl rings and/or cyclic chiral fragments. In order to accommodate the ring strain, the crystal structure of **6f** reveals significant bond-angle distortion at the triazole N1 position and the amide bond, as well as deconjugation of the aromatic and amide π systems (Figure 3). Compound **6h** represents a further escalation in conformational constraint, incorporating, as it does, three bridged rings within a 13-membered macrocycle. We suspect that conducting the macrocyclization at 150°C allows the precursors of these strained systems to populate the high-energy conformations required for ring closure. As indicated by **6i** and **j**, increasing the ring size from 12 to 14 significantly reduces the ring strain, resulting



Scheme 2. Substrate scope for the flow macrocyclization. Numbers in parentheses correspond to isolated yields after column chromatography. Reactions were conducted in a copper tube flow reactor at 0.0167 M in EtOH, in the presence of TTTA (10 mol%) and DIPEA (2 equiv), at 150 °C for 5 min. Boc = *tert*-butoxycarbonyl.

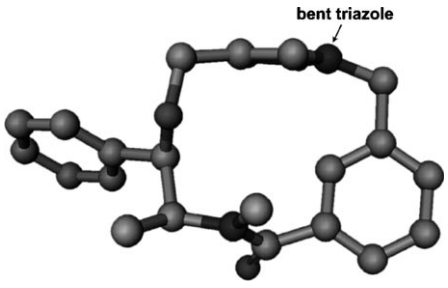


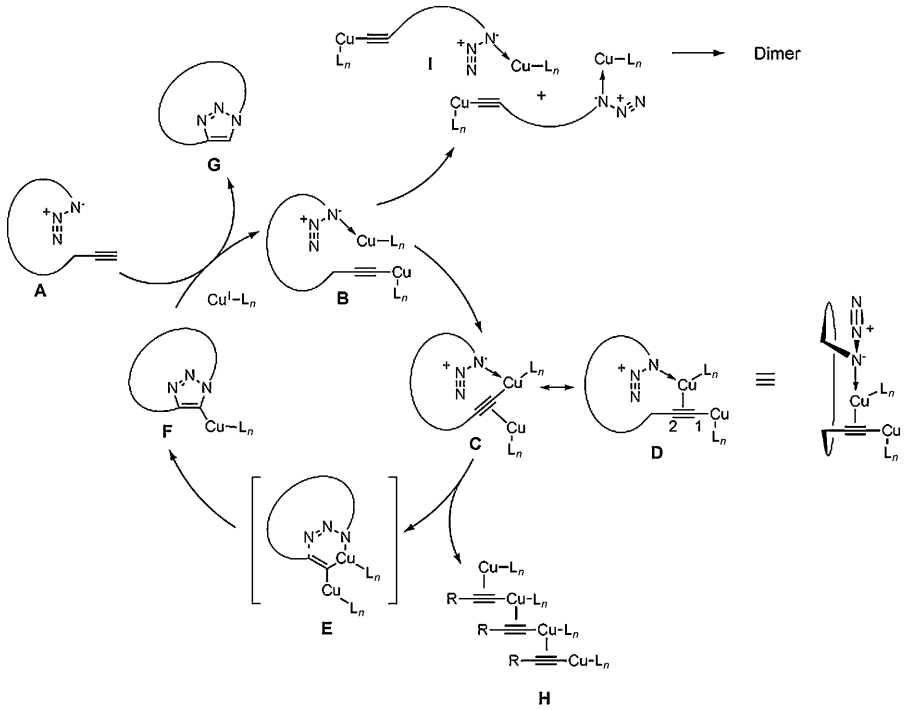
Figure 3. The X-ray crystal structure of macrocycle **6f** viewed edge-on to the triazole ring. Hydrogen atoms were omitted for clarity.

in a higher yielding reaction. Macrocycles **6k** and **l** are 14- and 16-membered rings, respectively, derived from Boc-L-hydroxyproline. These are produced in good yields, with the *N*-Boc protecting group surviving the elevated reaction temperature, and illustrate the potential for these macrocycles to serve as core fragments in library synthesis. Finally, **6m** and **n** illustrate the ability of this process to access larger macrocycles (18- and 22-membered rings, respectively) in good yield.

Based upon our findings, we believe the high ratio of macrocycle to dimer achieved in our flow protocol is the result of several factors. Firstly, in line with the elemental analysis results and the reactions conducted with soluble copper sources, the reaction appears to be occurring at or near to the copper surface (area 70 cm^2). Although we cannot be certain about the identity of the copper species involved in the copper-tube reaction, it is known that nanoscale clusters of copper atoms can catalyze this reaction,[18] and that copper metal can supply the necessary catalytic Cu^I species in the presence of mild oxidants such as alcohols.[16a] This involvement of the copper surface might be contributing to a "pseudodilution" effect, as has been observed for other macrocyclizations that use solid-supported reagents,[19] and thus an improved product ratio compared to the use of soluble copper ions (e.g. Table 1, entry 11 vs. Table 2, entries 5 and 9). This effect is thought to result from the interaction of the cyclization precursor with a surface-bound reagent, at sufficient distance from other surface-associated molecules to reduce the frequency of intermolecular reactions. It is possible, in our case, that the azido functional group plays a role in the interaction with a copper species on the reactor surface, since it has been demonstrated that organic azides can leach copper very effectively from a carbon support[12a] and can act as ligands for transition metals.[20]

A further significant factor is the presence of TTTA, which both accelerates the reaction and markedly improves the product ratio. TTTA is thought to accelerate the CuAAC reaction by generating a monomeric copper species, in this case, generated from the copper surface, thereby preventing the formation of nonproductive multimeric complexes of copper acetylides.[16a,21] This would certainly account for the significant rate increase we observed. Its impact on the product-to-dimer ratio might be a steric effect, in which the transition state for the intramolecular reaction (involving one molecule) is less crowded that that for the intermolecular reaction (involving two molecules). It is also possible that these two effects (surface interaction through the azide, together with a reactive, but sterically hindered copper–acetylide) act in concert.

A potential catalytic cycle for the reaction is outlined in Scheme 3. Interaction of azidoalkyne **A** with a copper species, in the presence of TTTA and base, yields surface-associated copper–acetylide adduct **B**. Although we cannot be sure about the nature of the ligands on the copper, one possibility would be for the azide to be ligated to a metallic copper cluster, and the copper acetylide to be complexed to TTTA. There is a growing case for the involvement of two copper species in the cycloaddition reaction[22] and so a further possibility is that the azide and alkyne become ligated to a common copper species as in **C** or **D**, each involving both σ- and π-bonded copper–alkyne species. Complexes **C** and **D** differ only with regard to which of the copper species



Scheme 3. The proposed catalytic cycle for the macrocyclization reaction.

is simultaneously ligated to both the azide and the alkyne. Most proposed mechanisms invoke an intermediate, such as **C**, in which the azide is jointly ligated to the σ-bonded copper species.[21] However, a π-bonded intermediate such as **D** has been proposed by Fokin and Hein in order to explain the experimental observation that the CuAAC reaction of iodoalkynes appears to proceed without breaking the C–I bond.[23] Furthermore, molecular modeling suggested to us that intermediate **D** might be sterically more accessible in conformationally constrained systems, such as those described here. It also offers an initial orthogonal approach of the azido-terminus to the alkyne double bond (as depicted in Scheme 3), as an alternative to the more strained "*exo*" conformation that has been proposed to account for the extensive macrocyclic dimerization observed by some groups.[14a] The structural distinction between **C** and **D** might not be significant in practice, given the ability of copper acetylides to exist in a wide range of structures, including μ-η_2-bonded systems.[22b]

The sequence is completed by cyclization via copper–alkylidene intermediate **E**. We presume that this step commits the reaction irreversibly to eventual triazole formation, trapping what appear (from X-ray crystallographic data) to be strained macrocycles in some cases. Reductive elimination of copper from metallocycle **E** leads to triazolo–copper intermediate **F**, which, upon protonation, yields product **G**. TTTA is presumably coordinated to the copper–acetylide during at least part of the sequence, reducing the likelihood of the reaction proceeding along either of the two potential nonproductive pathways to yield multimeric complexes **H** or dimers through the types of interaction depicted by **I**.

In principle, we see no reason why the outcomes we have achieved could not be reproduced in batch mode, provided that exposure to a large copper surface at elevated temperature is possible. However, our control experiments, using a large excess of copper turnings or copper powder (100-fold by weight, for example, 300 mg copper to 3 mg substrate) and an oil bath to heat the reaction mixture, have, thus far, not achieved the macrocycle-to-dimer ratio seen in our flow protocol. In fact, it appears impractical in batch processes to perfectly replicate the exposure to copper achieved by flowing the reaction mixture through a very long (3 m) and narrow (0.75 mm inner diameter) copper tube. Furthermore, the process of heating and stirring a reaction mixture in an open oil bath at 150 °C is much more hazardous than our fully contained flow reactor set up (particularly at scale). Whilst one could potentially use a microwave heater to achieve these elevated temperatures, we were unable to conduct satisfactory control experiments in such a system, since our laboratory is not equipped with the type of internal temperature sensor viewed as essential in order to measure and precisely control the temperature at the metal surface inside the microwave reactor.[10a] Our flow approach allows us to control the temperature precisely, to utilize a "green" solvent (ethanol) safely above its boiling point with no risk of glass vessels rupturing, and also avoids the contamination issues associated with a soluble transition-metal catalyst. Therefore, we believe that our approach represents a very efficient method of constructing this important class of molecules, in terms of yield, concentration, and environmental considerations.

Conclusion

We have developed a simple and efficient method for constructing druglike macrocycles at modest dilution in a flow chemistry protocol, by exploiting a copper-surface-catalyzed, azide–alkyne cycloaddition reaction. The method is "green", utilizing an environmentally friendly solvent, and a copper tube that requires no special preparation, poses no problems of catalyst recovery, and is completely reusable. The methodology allows access to a range of macrocyclic systems of comparable ring size to cyclic tetra- through hepta-peptides, including a number of unusual strained systems, but satisfy-

ing our aspiration of "druglike" with regard to functionality and physicochemical properties (for example, the Lipinski descriptors).[24]

Future work will extend this methodology to the construction of more densely functionalized systems and, in particular, the construction of macrocyclic libraries for use in screening against protein–protein interaction targets.

Experimental Section

Representative preparative-scale flow macrocyclization: Azidoalkyne **3a** (0.10 M in EtOH, 100 μL, 0.010 mmol, 1.0 equiv), TTTA (0.01 M in EtOH, 100 μL, 0.001 mmol, 0.10 equiv), DIPEA (0.1 M in EtOH, 200 μL, 0.020 mmol, 2.0 equiv), and EtOH (200 μL) were aspirated from their respective source vials, mixed through a PFA mixing tube (0.2 mm inner diameter), and loaded into an injection loop. The reaction segment was injected into the flow reactor, set at 150 °C, passed through the reactor at 300 μL min^{-1} (5 min residence time). A total of 20 reaction segments prepared in this manner were collected in a round bottom flask. Upon completion, the reaction mixture was concentrated and dried in vacuo. The crude reaction mixture was purified by using a Biotage Horizon automated flash column chromatography system (silica gel, EtOAc, $R_f = 0.27$) to yield **6a** as a white solid (45.6 mg, 73 %). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.60$ (s, 1H), 7.45 (d, $J = 7.5$ Hz, 2H), 7.35 (t, $J = 7.5$ Hz, 2H), 7.22–7.28 (m, 1H), 4.94 (d, $J = 13.2$ Hz, 1H), 4.77 (br s, 1H), 4.48–4.69 (m, 2H), 4.22–4.30 (m, 1H), 4.10–4.18 (m, 1H), 2.99 (br s, 1H), 2.53 (br s, 3H), 2.34 (br s, 1H), 2.07–2.21 (m, 2H), 0.81 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 172.4$, 145.6, 139.6, 128.2, 127.0, 126.0, 123.1, 78.0, 62.8, 55.8, 49.5, 31.8, 29.6, 24.1, 9.9 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{17}H_{22}N_4O_2$: 315.1815 $[M+H]^+$; found: 315.1819.

Acknowledgements

This work was funded by Pfizer Worldwide R&D, where K.J. is employed. The authors would like to thank Neal Sach and John Kath for invaluable advice, Jason Hein and Valery Fokin for helpful discussions and gifts of tris(triazole) catalysts, Khanh Tran and Kevin Freeman-Cook for generous supply of intermediates, Jeff Elleraas for chiral chromatography support, and Curtis Moore and Raj Chadha for crystallographic data.

[1] J. A. Wells, L. McClendon, *Nature* **2007**, *450*, 1001–1009.
[2] E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discovery* **2008**, *7*, 608–624.
[3] S. J. Stachel, C. A. Coburn, S. Sankaranarayanan, E. A. Price, B. L. Pietrak, Q. Huang, J. Lineberger, A. S. Espeseth, L. Jin, J. Ellis, M. K. Holloway, S. Munshi, T. Allison, D. Hazuda, A. J. Simon, S. L. Graham, J. P. Vacca, *J. Med. Chem.* **2006**, *49*, 6147–6150.
[4] R. J. Cherney, L. Wang, D. T. Meyer, C. B. Xue, Z. R. Wasserman, K. D. Hardman, P. K. Welch, M. B. Covington, R. A. Copeland, E. C. Arner, W. F. DeGrado, C. P. Decicco, *J. Med. Chem.* **1998**, *41*, 1749–1751.
[5] K. X. Chen, F. G. Njoroge, A. Arasappan, S. Venkatraman, B. Vibulbhan, W. Yang, T. N. Parekh, J. Pichardo, A. Prongay, K. C. Cheng, N. Butkiewicz, N. Yao, V. Madison, V. Girijavallabhan, *J. Med. Chem.* **2006**, *49*, 995–1005.
[6] a) Only four of the top 200 pharmaceutical products by sales (2008) are macrocycles [prograf (tacrolimus), sandimmune (cyclosporine), sandostatin (octreotide), and klacid (clarithromycin)], the first three of which are natural-product derived and the fourth is a cyclic peptide; b) a search of the NIH PubMed database (over 68 million entries) for compounds containing six-membered lactam rings (all other ring atoms carbon) on April 23rd, 2010 generated 169580 hits (0.25 %); in contrast, analogous searches for compounds containing 13-membered and 18-membered lactams yielded 127 (1.86×10^{-4} %) and 9 hits (1.3×10^{-5} %), respectively.
[7] L. A. Wessjohann, E. Ruijter, *Top. Curr. Chem.* **2005**, *243*, 137–184.
[8] A survey of 158 macrocyclization reactions published during 2009 revealed that the median concentration employed was 0.002 M and that the most common concentration employed was 0.0005 M. The two most common macrocyclization reactions were macrolactamization and macrolactonization.
[9] a) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312; b) A. D. Curzons, D. J. C. Constable, D. N. Mortimer, V. L. Cunningham, *Green Chem.* **2001**, *3*, 1; c) D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.* **2002**, *4*, 521.
[10] For recent selected reviews, see: a) T. Razzaq, C. O. Kappe, *Chem. Asian J.* **2010**, *5*, 1274–1289; b) K. Geyer, T. Gustafson, P. H. Seeberger, *Synlett* **2009**, 2382–2391; c) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495–2507; d) C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, *1655*–1671; e) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151–163; f) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733–740; g) P. Watts, C. Wiles, *Chem. Commun.* **2007**, 433–467; h) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318; i) J. Kobayashi, Y. Mori, S. Kobayashi, *Chem. Asian J.* **2006**, *1*, 22–35.
[11] A. R. Bogdan, N. W. Sach, *Adv. Synth. Catal.* **2009**, *351*, 849–854.
[12] For recent selected examples, see: a) M. Fuchs, W. Goessler, C. Pilger, C. O. Kappe, *Adv. Synth. Catal.* **2010**, *352*, 323–328; b) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem.* **2009**, *121*, 4077–4081; *Angew. Chem. Int. Ed.* **2009**, *48*, 4017–4021; c) C. D. Smith, I. R. Baxendale, G. K. Tranmer, M. Baumann, S. C. Smith, R. A. Lewthwaite, S. V. Ley, *Org. Biomol. Chem.* **2007**, *5*, 1562–1568; d) C. D. Smith, I. R. Baxendale, S. Lanners, J. J. Hayward, S. C. Smith, S. V. Ley, *Org. Biomol. Chem.* **2007**, *5*, 1559–1561.
[13] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; c) P. Wu, V. V. Fokin, *Aldrichimica Acta* **2007**, *40*, 7–17.
[14] For recent selected examples of peptidic and nonpeptidic macrocycle synthesis through CuAAC reactions, see: a) Yu. L. Angell, K. Burgess, *Chem. Soc. Rev.* **2007**, *36*, 1674–1689, and references therein; b) A. Rowley Kelly, J. Wei, S. Kesavan, J.-C. Marie, N. Windmon, D. W. Young, L. A. Marcaurelle, *Org. Lett.* **2009**, *11*, 2257–2260; c) S. Muthana, H. Yu, H. Cao, J. Cheng, X. Chen, *J. Org. Chem.* **2009**, *74*, 2928–2936; d) S. Binauld, C. J. Hawker, E. Fleury, E. Drockenmuller, *Angew. Chem.* **2009**, *121*, 6782–6786; *Angew. Chem. Int. Ed.* **2009**, *48*, 6654–6658; e) G. V. Latyshev, M. S. Baranov, A. V. Kazantsev, A. D. Averin, N. V. Lukashev, I. P. Beletskaya, *Synthesis* **2009**, 2605–2615; f) J. E. H. Day, S. Y. Sharp, M. G. Rowlands, W. Aherne, P. Workman, C. J. Moody, *Chem. Eur. J.* **2010**, *16*, 2758–2763; g) T. Pirali, V. Faccio, R. Mossetti, A. A. Grolla, S. Di Micco, G. Bifulco, A. A. Genazzani, G. C. Tron, *Mol. Diversity* **2010**, *14*, 109–121; h) J. M. Holub, K. Kirshenbaum, *Chem. Soc. Rev.* **2010**, *39*, 1325–1337.
[15] a) For a recent example of catalysis by a copper surface under flow and microwave heating, see: G. Shore, W. J. Yoo, C. J. Li, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 126–133; b) for a recent example of desorption and readsorption from a metal (palladium) surface, see: S. MacQuarrie, J. H. Horton, J. Barnes, K. McEleney, H. P. Loock, C. M. Crudden, *Angew. Chem.* **2008**, *120*, 3324–3328; *Angew. Chem. Int. Ed.* **2008**, *47*, 3279–3282.
[16] a) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302–1315; b) T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853–2855.
[17] F. E. Valera, M. Quaranta, A. Moran, J. Blacker, A. Armstrong, J. T. Cabral, D. G. Blackmond, *Angew. Chem.* **2010**, *122*, 2530–2537; *Angew. Chem. Int. Ed.* **2010**, *49*, 2478–2485.

[18] For a recent example, see: F. Alonso, Y. Moglie, G. Radivoy, M. Yus, *Eur. J. Org. Chem.* **2010**, *10*, 1875–1884.
[19] E. Gonthier, R. Breinbrauer, *Mol. Diversity* **2005**, *9*, 51–62.
[20] a) M. Barz, E. Herdtweck, W. R. Thiel, *Angew. Chem.* **1998**, *110*, 2380–2383; *Angew. Chem. Int. Ed.* **1998**, *37*, 2262–2265; b) H. V. Rasika Dias, S. A. Polach, S.-K. Goh, E. F. Archibong, D. S. Marynick, *Inorg. Chem.* **2000**, *39*, 3894–3901.
[21] V. O. Rodionov, S. I. Presolski, D. Díaz Díaz, V. V. Fokin, M. G. Finn, *J. Am. Chem. Soc.* **2007**, *129*, 12705–12712.
[22] a) M. Ahlquist, V. V. Fokin, *Organometallics* **2007**, *26*, 4389–4391; b) B. F. Straub, *Chem. Commun.* **2007**, *3868*–3870.
[23] J. E. Hein, J. C. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem.* **2009**, *121*, 8162–8165; *Angew. Chem. Int. Ed.* **2009**, *48*, 8018–8021.
[24] a) C. A. Lipinski, F. I. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25; b) C. A. Lipinski, *Drug Discovery Today* **2004**, *9*, 337–341.

Received: August 3, 2010
Published online: October 29, 2010

