The Efficient Construction of Macrocycles Using Copper Surface-Catalyzed Click Reactions in Flow

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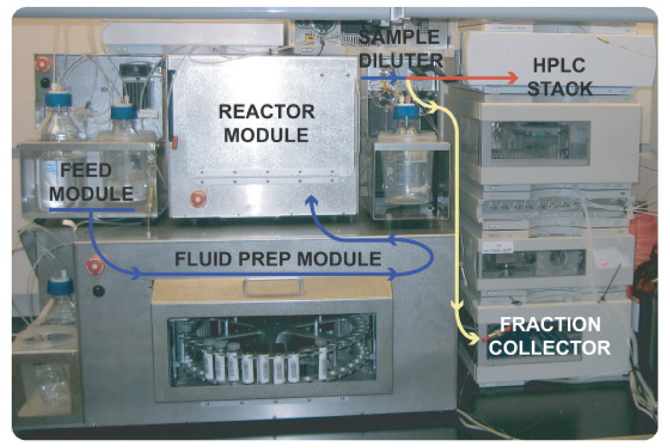
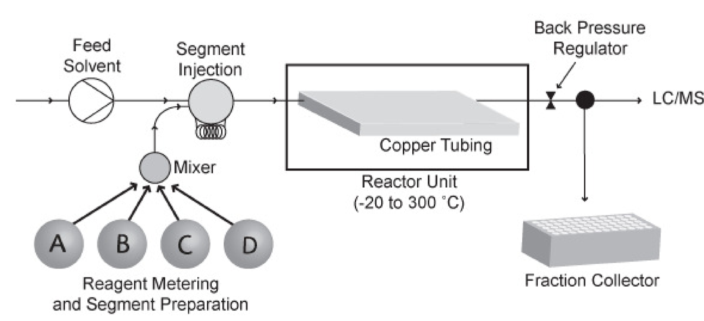
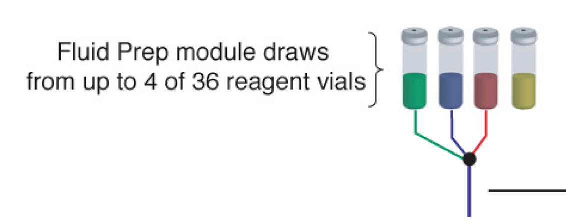
Introduction

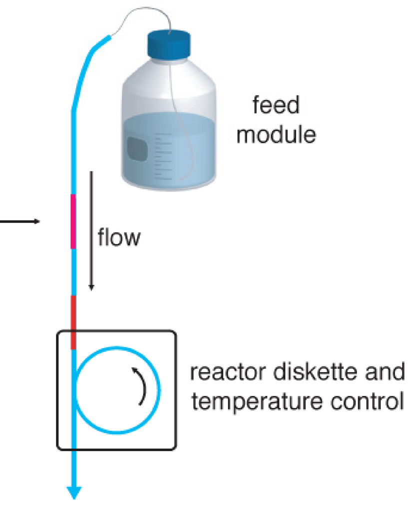
Conjure Flow Reactor



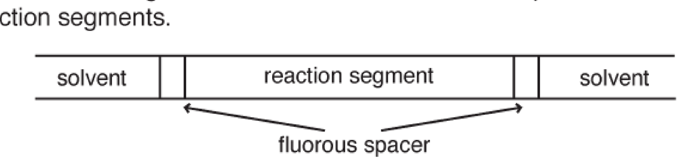


The Conjure flow reactor was designed to operate on a scale suitable for both medicinal chemistry and process research. The instrument adopts a segmented flow approach versus a continuous stream approach in order to minimize material consumption and limit reaction size. Such reactor systems are suitable for both reaction optimization and preparative scale chemistry, and designed to withstand both elevated temperatures and pressures. The Conjure's Fluid Prep module enables up to 4 of 36 reagents to be used in a reaction segment, enabling facile library development and reaction screening.



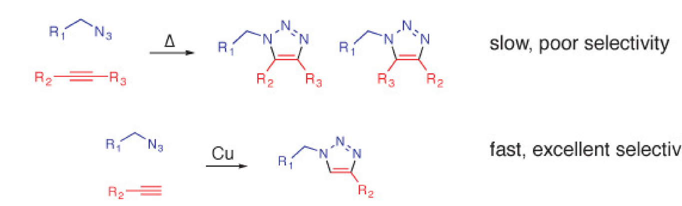


Discrete reaction segments are inserted and maintained in flow using an immiscible fluorous spacer (perfluoromethyldecalin). Small plugs of spacer prevent the reaction segment from diffusing into the bulk reaction solvent and prevent contamination between reaction segments.



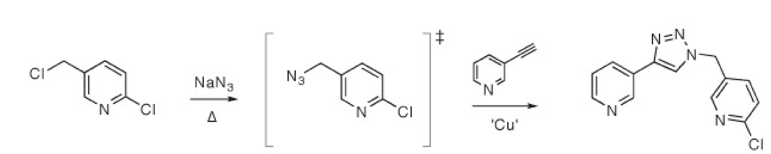
Copper Flow Reactor for Triazole Syntheses

Traditional Click Chemistry

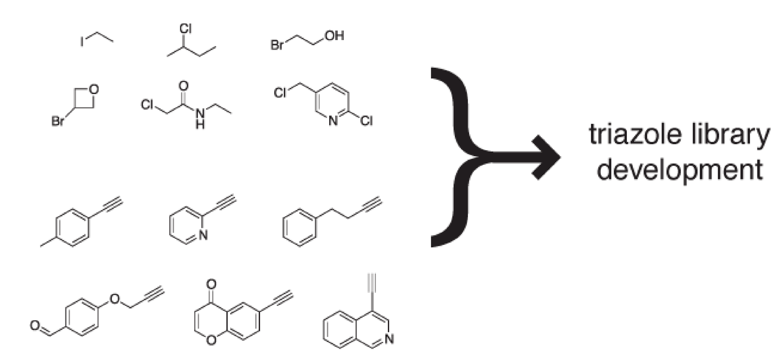


The copper-catalyzed 1,3-dipolar cycloaddition, also known as the 'click reaction,' has gained a considerable amount of attention since its discovery in 2001. The thermal addition of organic azides to alkynes is slow and has poor selectivity, whereas the copper-catalyzed reaction is fast and selective. Reactions, however, are generally performed starting with unstable organic azides.

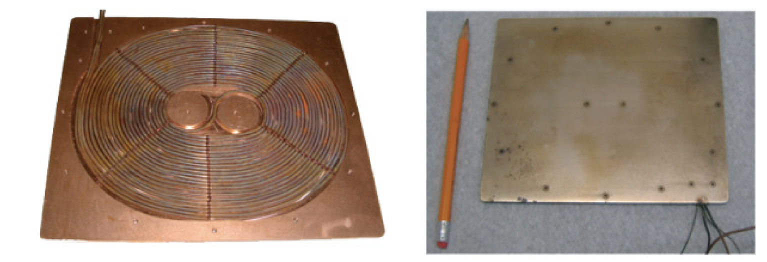
Flow Reactor Enabled One-Pot Click Reaction



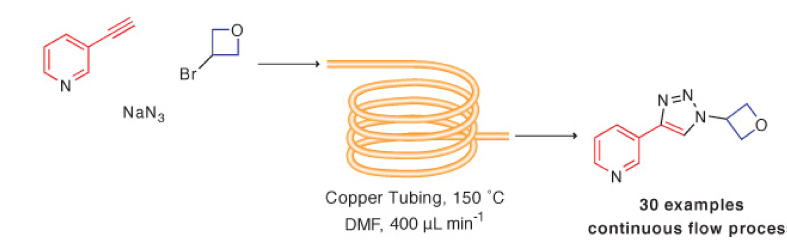
The ability to generate organic azides in situ from alkyl halides would be a significant advantage, as it would reduce the risks associated with their isolation and storage. Furthermore, this in situ preparation would greatly increase the number of organic azides that can be used in the 'click reaction.'



Copper Flow Reactor Diskettes



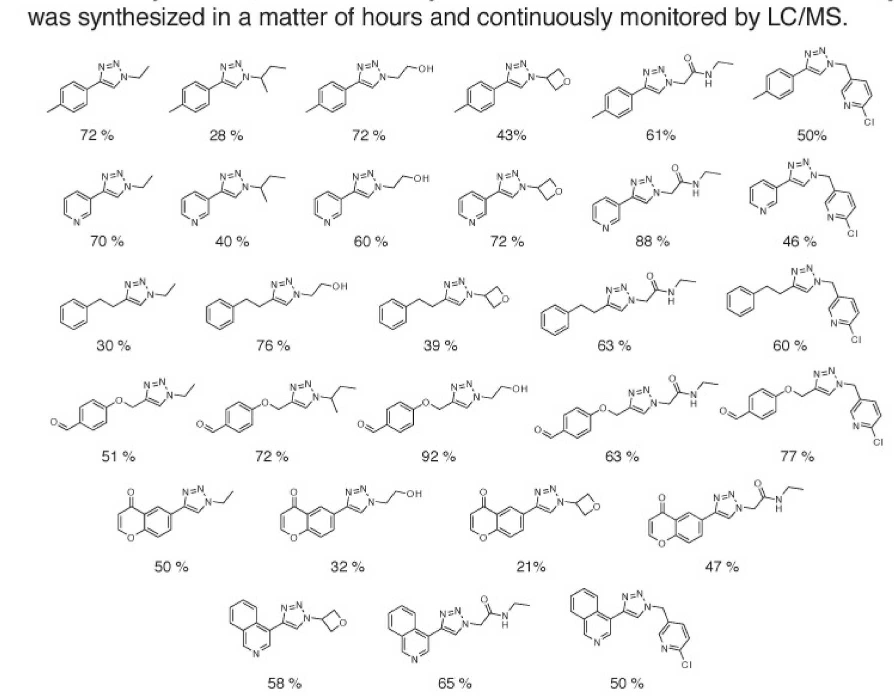
The reactor diskette consists of copper tubing (0.75 mm i.d.) coiled between two copper plates (145 mm x 165 mm x 5 mm). The diskette was used in hundreds of trials without any loss of activity and proved effective in other copper-catalyzed transformations such as Sonogashira and Ullman couplings.



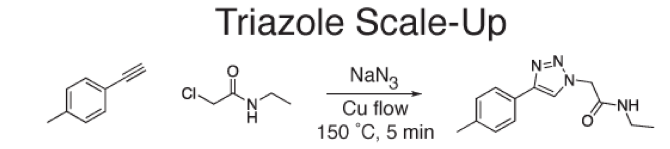
Using the Conjure Flow Reactor, a one-pot click methodology was developed. Solutions of alkyne, alkyl halide and sodium azide were aspirated from source vials, mixed, and injected into the reactor as a discrete reaction segment. A fluorous spacer injected between reaction segments enables multiple reactions to be passed through the reactor at once, maximizing the system output and enabling rapid library development. The reactor consists of copper tubing and a heating element. The copper tubing is essential to catalyze the cycloaddition. Upon exiting the reactor, reaction segments are analyzed using an ultra-fast LC/MS to give a real-time report of product distributions.

Continuous Flow Triazole Library Synthesis

Using the Conjure Flow Reactor, a library of triazoles was synthesized starting from six alkyl halides, six terminal alkynes and sodium azide. The triazole library was synthesized in a matter of hours and continuously monitored by LC/MS.



Triazole Scale-Up



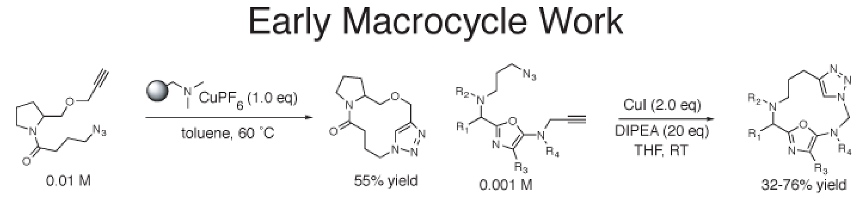
Scaling up using the Conjure flow reactor is a function of time; if more product is needed, the system is run for a longer period of time. No reengineering is required when increasing the scale of flow reactions.

Time	Output
12 min	115 mg
1 hour	575 mg
1 day	13.8 g

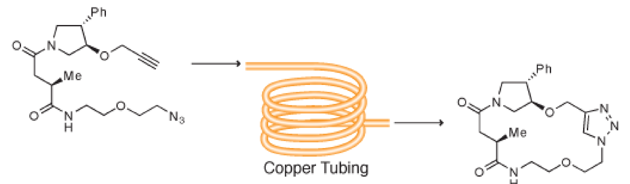
Bogdan, A. R. et al., *Adv. Synth. Catal.* **2009**, *351*, 849.

Synthesis of Macrocycles in Flow

Early Macrocycle Work

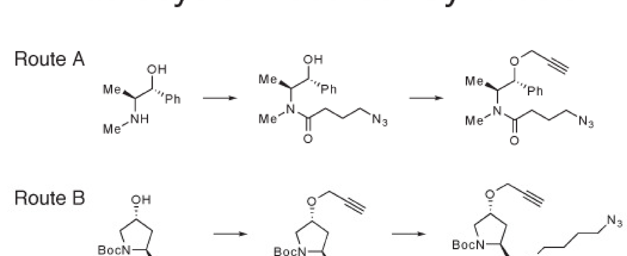


Protein-protein interactions represent a critically important sub-set of molecular interactions which are poorly addressed by current small molecule drug design strategies. Macrocyclic systems offer a compelling approach to modulating these challenging targets, since their intrinsic conformational constraint and lower rotatable bond count offers the prospect of improved physicochemical, pharmacological and pharmacokinetic performance compared to their acyclic analogs. Methodologies to synthesize these promising compounds are underdevleloped, however, typically resorting to high dilution and high catalyst loadings to achieve high yields.



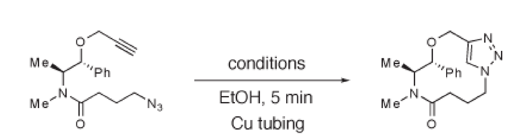
We report a new approach for the efficient construction of a series of prototypical 'drug-like' macrocycles, without resorting to extremely high dilution conditions, through the implementation of high temperature 'click' reaction in flow. To the best of our knowledge, this represents the first report of a macrocyclic closure under flow conditions.

Macrocycle Precursor Synthesis

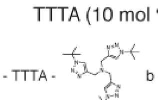


Our aim was to construct a small library of macrocycles of varying ring size and functionality, available via short synthetic sequences (3-4 steps) from readily available, chiral, bifunctional starting materials such as amino alcohols (Route A) and hydroxy-acids (Route B).

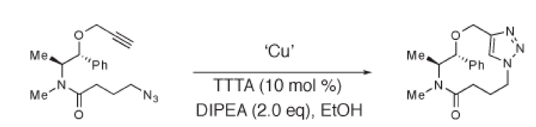
Macrocycle Optimization



Additive	[SM]	T (°C)	% Prod (UV)	Prod:Dimer
-	0.1	150	13	0.34:1.0
-	0.05	150	13	0.37:1.0
-	0.033	150	17	0.39:1.0
-	0.0167	150	24	0.44:1.0
TTTA[a] (10 mol %)	0.0167	150	72	2.6:1.0
TTTA (10 mol %), DIPEA (2.0 eq)	0.0167	150	79 [73][b]	4.6:1.0

a - TTTA -  b - isolated yield

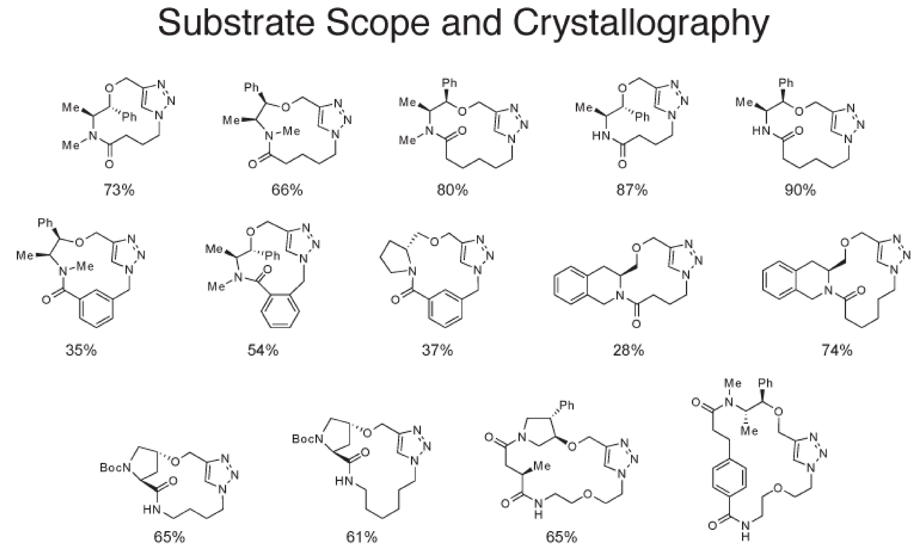
Flow vs. Batch Macrocyclizations

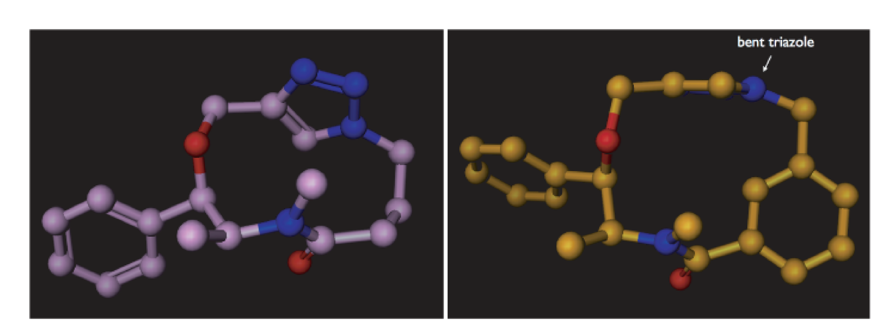


Conditions	% Prod (UV)	Prod:Dimer
Cu turnings (1.0 eq), reflux, 5 min	NR	-
CuI (1.0 eq), reflux, 5 min	20	1.1:1.0
Cu turnings (100 wt eq), 150 °C, 5 min	17	1.1:1.0
CuI (1.0 eq), 150 °C, 5 min	52	1.5:1.0
no copper, 150 °C, 5 min, Hastelloy tubing, flow	<5	n.d.
CuI (1.0 eq), 150 °C, 5 min, Hastelloy tubing, flow	68	2.6:1.0
CuI (0.004 eq), 150 °C, 5 min, Hastelloy tubing, flow	35	n.d.

A series of batch reactions, using both soluble and insoluble copper catalysts, were performed to try to replicate the results using the copper tubing from the flow reactor. While high yields could be obtained, excess copper catalyst had to be added to the reaction to get these results.

Substrate Scope and Crystallography



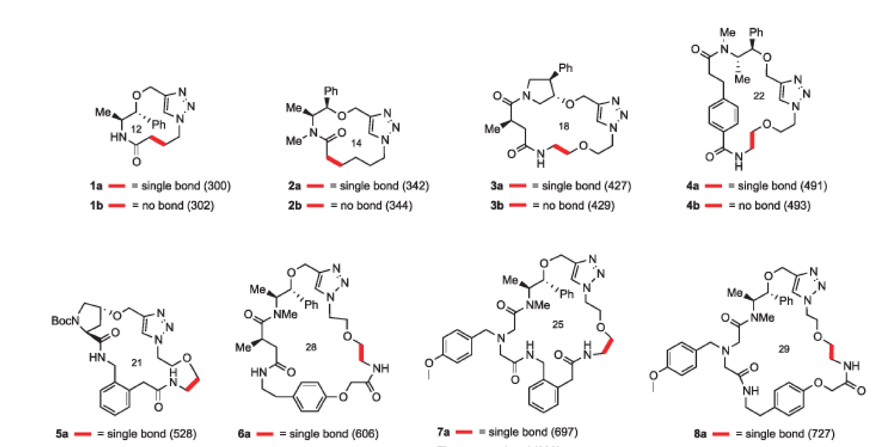


A series of 12- to 22-membered rings were synthesized in modest to excellent isolated yields. In all cases, the macrocycles were synthesized at the same concentration (0.0167 M) at 150 °C in the copper flow reactor. We suspect that conducting the macrocyclization at 150 °C is allowing the precursors of strained systems to populate the high-energy conformations necessary for macrocyclization. In order to accommodate the ring strain, the crystal structure above reveals significant bond angle distortion at the triazole N-1 position and amide bond, as well as deconjugation of the aromatic and amide π-systems.

Bogdan, A. R. et al., *Chem. Eur. J.* **2010**, *16*, 14506.

Diffusion Rates of Macrocycles

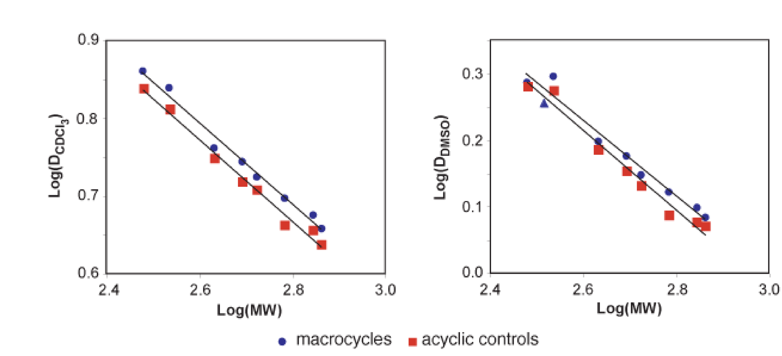
We have conducted a systematic study of the impact of macrocyclization on the diffusion behavior of drug-like molecules. A set of carefully matched-pairs of macrocycles and acyclic controls were designed to provide a strict comparison in terms of functionality, polarity and molecular weight. We find a consistent, statistically significant increase in diffusion rate for the macrocycle set versus their acyclic controls, which appears independent of molecular weight over the range studied. Using both the intramolecular and intermolecular click reactions previously discussed, macrocycles and acyclic controls ranging from 12- to 29-membered rings and a MW of 300 to 730 were synthesized efficiently in flow.



$$D = \frac{k_B T}{6\pi\eta R_H}$$

D : diffusion coefficient
k_B : Boltzmann constant
T : temperature
η : solvent viscosity
R_H : hydrodynamic radius

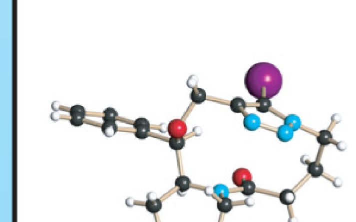
The Einstein-Stokes equation states that molecular diffusion (**D**) is inversely proportional to hydrodynamic radius (**R_H**). It is predicted that the conformational constraint of the macrocycle will lower the **R_H**, which in turn increases the rate of molecular diffusion.



Molecular diffusion was measured by ^{1}H NMR using a bipolar pulse longitudinal eddy current delay (BPPLED) method. In both high dielectric (DMSO) and low dielectric ($CHCl_3$) solvents, we were able to demonstrate a clear increase in diffusion rate for the macrocycles relative to their acyclic controls.

Bogdan, A. R. et al., *submitted.*

Future Work



The synthesis of iodotriazole macrocycles using flow chemistry. Preliminary results indicate the conversion of azido-iodoalkynes to iodotriazole macrocycles after 10 minutes at 100 °C.

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