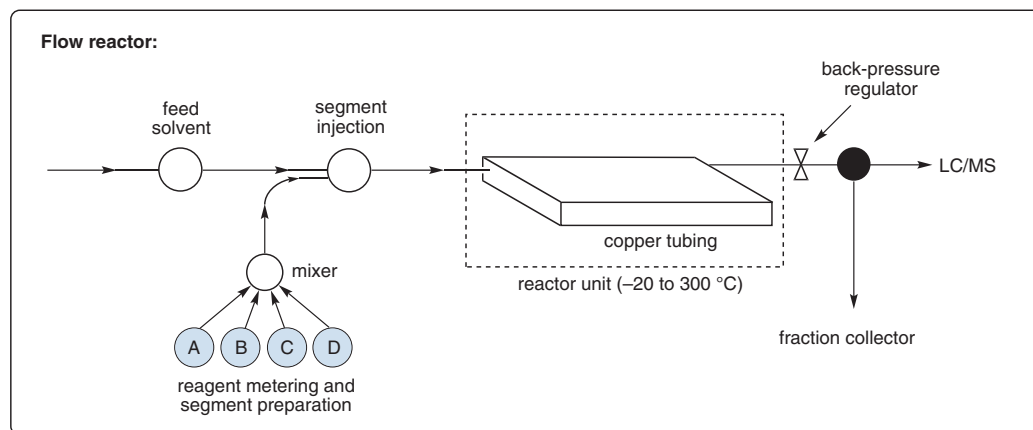
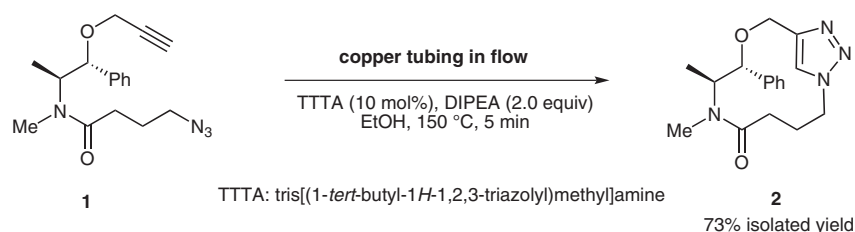


## Flow Macrocyclization Using Copper Tubing



**Flow macrocyclization reaction:**



**Significance:** Flow macrocyclization with a copper surface catalyst via the azide–acetylene cycloaddition reaction was described. The flow macrocyclization of an azidealkyne **1** with TTTA and DIPEA was performed in copper tubing (3 m length, 0.75 mm inner diameter) to give the triazole-containing macrocycle **2** in 73% isolated yield within five minutes of residence time without addition of extraneous copper(I) salt in the reaction mixture. The structure of the 12-membered macrocycle **2** was confirmed by X-ray crystallography.

**Comment:** A series of 12- to 22-membered macrocycles was prepared under similar flow conditions (14 examples, 28–90% yield). Elemental analysis in the ethanolic reaction mixture indicated less than 5 ppm of copper. In flask reactions, refluxing the reaction mixture of azidealkyne **1**, TTTA, and DIPEA in ethanol with copper turnings gave no detectable product **2** after five minutes, and only a trace amount of **2** after 90 min. Under similar conditions, CuI (0.2 or 1.0 equiv) was also not effective.