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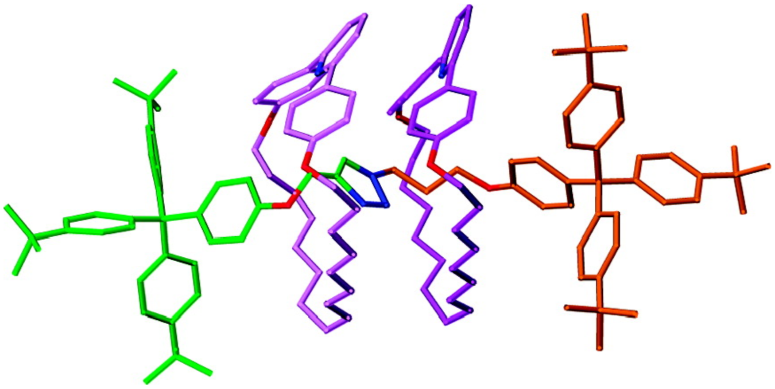

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Catalytic “Active-Metal” Template Synthesis of [2]Rotaxanes, [3]Rotaxanes, and Molecular Shuttles, and Some Observations on the Mechanism of the Cu(I)-Catalyzed Azide−Alkyne 1,3-Cycloaddition

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Abstract: A synthetic approach to rotaxane architectures is described in which metal atoms catalyze covalent bond formation while simultaneously acting as the template for the assembly of the mechanically interlocked structure. This “active-metal” template strategy is exemplified using the Huisgen−Meldal−Fokin Cu(I)-catalyzed 1,3-cycloaddition of azides with terminal alkynes (the CuAAC “click” reaction). Coordination of Cu(I) to an endotopic pyridine-containing macrocycle allows the alkyne and azide to bind to metal atoms in such a way that the metal-mediated bond-forming reaction takes place through the cavity of the macrocycle—or macrocycles—forming a rotaxane. A variety of mono- and bidentate macrocyclic ligands are demonstrated to form [2]rotaxanes in this way, and by adding pyridine, the metal can turn over during the reaction, giving a catalytic active-metal template assembly process. Both the stoichiometric and catalytic versions of the reaction were also used to synthesize more complex two-station molecular shuttles. The dynamics of the translocation of the macrocycle by ligand exchange in these two-station shuttles could be controlled by coordination to different metal ions (rapid shuttling is observed with Cu(I), slow shuttling with Pd(II)). Under active-metal template reaction conditions that feature a high macrocycle:copper ratio, [3]-rotaxanes (two macrocycles on a thread containing a single triazole ring) are also produced during the reaction. The latter observation shows that under these conditions the mechanism of the Cu(I)-catalyzed terminal alkyne−azide cycloaddition involves a reactive intermediate that features at least two metal ions.

Introduction

Most noncovalent bond directed approaches[1] to rotaxanes developed to date require at least stoichiometric quantities of a template which often involves pre-established strongly binding recognition motifs that “live on” [2] in the mechanically interlocked molecule that is formed. Besides holding the reactive fragments in an orientation that directs interlocking, the template is generally otherwise passive during the reaction. Building on the principles of transition-metal catalysis, we recently[3] began to explore a strategy in which template ions could also play an active role in promoting the crucial final covalent bond forming reaction that captures the interlocked structure (i.e., the metal has a dual function, acting as a template for entwining the precursors *and* catalyzing covalent bond formation between the reactants). This “active-metal” [4] template process is shown schematically in Figure 1 in both stoichiometric (1 equiv of

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(1) For reviews which highlight various aspects of template strategies to rotaxanes, see: (a) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725−2828. (b) *Molecular Catenanes, Rotaxanes and Knots: A Journey Through the World of Molecular Topology*; Sauvage, J.-P., Dietrich-Buchecker, C., Eds.; Wiley-VCH: Weinheim, Germany, 1999. (c) Breault, G. A.; Hunter, C. A.; Mayers, P. C. *Tetrahedron* **1999**, *55*, 5265−5293. (d) *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2000. (e) Hubin, T. J.; Busch, D. H. *Coord. Chem. Rev.* **2000**, *200*, 5−52. (f) Raehm, L.; Hamilton, D. G.; Sanders, J. K. M. *Synlett* **2002**, 1743−1761. (g) Kim, K. *Chem. Soc. Rev.* **2002**, *31*, 96−107. (h) Aricó, F.; Badjić, J. D.; Cantrill, S. J.; Flood, A. H.; Leung, K. C.-F.; Liu, Y.; Stoddart, J. F. *Top. Curr. Chem.* **2005**, *249*, 203−259. (i) Dietrich-Buchecker, C.; Colasson, B. X.; Sauvage, J.-P. *Top. Curr. Chem.* **2005**, *249*, 261−283. (j) Kay, E. R.; Leigh, D. A. *Top. Curr. Chem.* **2005**, *262*, 133−177. (k) Loeb, S. J. *Chem. Commun.* **2005**, 1511−1518. (l) Bogdan, A.; Rudzevich, Y.; Vysotsky, M. O.; Böhmer, V. *Chem. Commun.* **2006**, 2941−2952. (m) Nitschke, J. R. *Acc. Chem. Res.* **2007**, *40*, 103−112. (n) Vickers, M. S.; Beer, P. D. *Chem. Soc. Rev.* **2007**, *36*, 211−225. (o) Loeb, S. J. *Chem. Soc. Rev.* **2007**, *36*, 226−235. For reviews on polyrotaxanes, see: (p) Harada, A. *Acta Polym.* **1998**, *49*, 3−17. (q) Takata, T.; Kihara, N.; Furusho, Y. *Adv. Polym. Sci.* **2004**, *171*, 1−75. (r) Huang, F.; Gibson, H. W. *Prog. Polym. Sci.* **2005**, *30*, 982−1018. (s) Wenz, G.; Han, B.-H.; Müller, A. *Chem. Rev.* **2006**, *106*, 782−817.

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(3) Aucagne, V.; Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186−2187.

(4) We use “active template” as a general term to describe a reaction in which a moiety both catalyzes covalent bond formation and acts as a template for the assembly of a particular structure. The term “active-metal template” describes a subset of active-template reactions in which the “active” moiety is a metal. A “catalytic active-metal template” reaction is one in which the metal catalyst turns over; a “stoichiometric active-metal template” reaction is one in which it does not.

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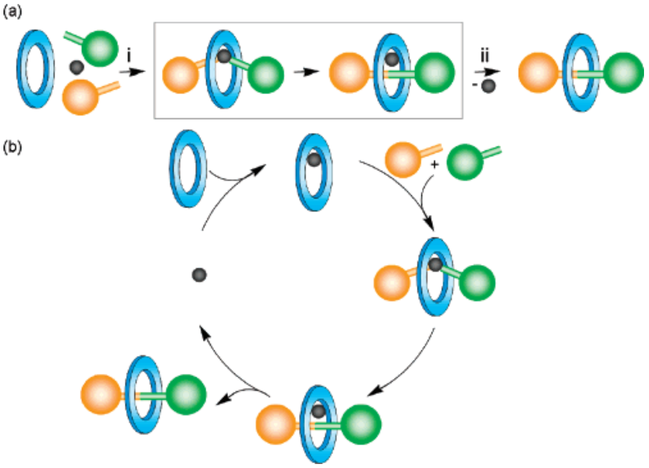

Figure 1. "Active-template" strategy to rotaxane architectures. The formation of a covalent bond between the green and orange "stoppered" units to generate the thread is promoted by the catalyst (shown in gray) and directed through the cavity of the macrocycle (shown in blue) by the catalyst's coordination requirements. (a) Stoichiometric active-metal template synthesis of a [2]rotaxane: (i) template assembly and covalent bond forming catalysis, (ii) subsequent demetalation. (b) Catalytic active-metal template synthesis of a [2]rotaxane.

the active template is required) and catalytic (the active template turns over during the reaction) forms. There are several potentially attractive features of such a synthetic approach to mechanically interlocked architectures, including (i) the inherent efficiency of a reaction in which the macrocycle−metal complex performs multiple functions, (ii) the lack of a requirement for permanent recognition elements in each component of the interlocked product, which increases the structural diversity possible in catenanes and rotaxanes and enables their formation to be "traceless", (iii) in some cases only substoichiometric quantities of the active template may be required (i.e., the catalytic active-metal template variant, Figure 1b), (iv) the strategy could prove applicable to many different types of well-known transition-metal-catalyzed (and even organocatalytic) reactions, (v) reactions that *only* proceed through a threaded intermediate would allow access to several currently inaccessible mechanically linked macromolecular architectures, and, finally, (vi) the coordination requirements during key stages of the catalytic cycle of active-template reactions could provide insight into the mechanisms of the catalyzed reactions.

Since the preliminary report[3] appeared on the realization of this strategy for rotaxane formation utilizing the Cu(I)-catalyzed[5−7] 1,3-cycloaddition[8] of organic azides and terminal alkynes (the CuAAC "click"[9,10] reaction), we have been delighted to see the concept be quickly adopted[11] to make rotaxanes[12] with other Cu(I)-catalyzed reactions, including alkyne-homocoupling and C−S bond forming reactions.[13,14] Here we expand on our investigation of the original system, showing that the active-metal template rotaxane-forming CuAAC reaction works well for both mono- and bidentate pyridine-containing macrocyclic ligands and can also be used to synthesize more complex two-station degenerate molecular shuttles whose interstation shuttling can be controlled by coordination to different metal ions. Furthermore, using a high macrocycle:copper ratio, [3]rotaxanes with two macrocycles on a single thread are somewhat unexpectedly produced during the active-metal template reaction. Together with some simple kinetic studies carried out under various rotaxane- and thread-forming reaction conditions, these experimental results provide some insight into the mechanism of the CuAAC reaction.

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(8) (a) *1,3-Dipolar Cycloadditions Chemistry*; Huisgen, R., Ed.; Wiley: New York, 1984; Vol. 1, pp 1−176. (b) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613−628.

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(10) A listing of examples of the use of "click" reactions is available at http://www.scripps.edu/chem/sharpless/click.html.

(11) Indeed, it was predicted[3] that, "Chelation to catalytic centers could lead to rotaxane- and catenane-forming protocols based on other metal-mediated reactions, including cross-couplings, condensations, and other cycloaddition reactions". For a recent example involving Pd(II)-catalyzed alkyne homo-couplings, see: Berná, J.; Crowley, J. D.; Goldup, S. M.; Hänni, K. D.; Lee, A.-L.; Leigh, D. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5709−5713.

(12) For the synthesis of rotaxanes and catenanes using the CuAAC reaction in "passive" template stoppering or macrocyclization protocols, see: (a) Mobian, P.; Collin, J.-P.; Sauvage, J.-P. *Tetrahedron Lett.* **2006**, *47*, 4907−4909. (b) Dichtel, W. R.; Miljanić, O. Š.; Spruell, J. M.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10388−10390. (c) Miljanić, O. Š.; Dichtel, W. R.; Mortezaei, S.; Stoddart, J. F. *Org. Lett.* **2006**, *8*, 4835−4838. (d) Aprahamian, I.; Dichtel, W. R.; Ikeda, T.; Heath, J. R.; Stoddart, J. F. *Org. Lett.* **2007**, *9*, 1287−1290; (e) Braunschweig, A. B.; Dichtel, W. R.; Miljanić, O. Š.; Olson, M. A.; Spruell, J. M.; Khan, S. I.; Heath, J. R.; Stoddart, J. F. *Chem. Asian J.* **2007**, *2*, 634−647.

(13) Saito, S.; Takahashi, E.; Nakazono, K. *Org. Lett.* **2006**, *8*, 5133−5136.

(14) Saito et al. imply[13] that the concept of binding of a substrate in a cavity while simultaneously activating it to catalysis is an extension of Vögtle's anion template route to rotaxanes [(a) Seel, C.; Vögtle, F. *Chem.*−*Eur. J.* **2000**, *6*, 21−24]. Actually the two strategies are rather fundamentally different. In the Vögtle reaction the macrocycle does not increase the reactivity of any of the building blocks for the rotaxane. In fact, the hydrogen bonding of the macrocycle to the phenoxide anion, combined with the steric hinderance conferred by the presence of the macrocycle, greatly *decreases* its reactivity. The only reason that rotaxane is formed in the Vögtle system is that the more reactive unthreaded phenoxide anion is completely insoluble under the reaction conditions. The active-template strategy described in ref 3 and elaborated upon in this paper has much more in common with Sauvage's original (passive) metal template ideas combined with Mock's [(b) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302−5308] and later Steinke's [(c) Tuncel, D.; Steinke, J. H. G. *Chem. Commun.* **1999**, 1509−1510. (d) Tuncel, D.; Steinke, J. H. G. *Chem. Commun.* **2002**, 496−497. (e) Tuncel, D.; Steinke, J. H. G. *Macromolecules* **2004**, *37*, 288−302] use of curcubituril to accelerate a reaction within a macrocycle cavity to form rotaxanes.

Cu(I)-Catalyzed Terminal Alkyne−Azide Cycloaddition (CuAAC Reaction)

Recently, there has been a tremendous surge of interest in so-called click[9,10] methodologies for functional molecule synthesis, the most popular of which is the Huisgen−Meldal−Fokin[15] Cu(I)-catalyzed 1,3-cycloaddition of organic azides with terminal alkynes (the CuAAC reaction).[5−7] The most common catalyst systems for this reaction employ water or alcohol solvents and use a Cu(II) salt in the presence of a reducing agent (often sodium ascorbate) to generate the required Cu(I) catalyst in situ.[5b,7a] Metallic copper[5b,7a] or copper clusters[16] have also been employed as precatalysts, and in some cases Cu(I) salts can be used directly. However, in apolar solvents Cu(I) salts usually require the presence of nitrogen[5b,7a,17] or phosphorus[18] ligands, or acetonitrile as a cosolvent, to stabilize the Cu(I) oxidation state, and undesired alkyne−alkyne homocoupling products are often observed under such reaction conditions.[5b,7a]

The basic mechanism of the CuAAC reaction is believed to be that shown in Scheme 1. A [2+3] cycloaddition—the mechanism of the thermal (i.e., uncatalyzed) Huisgen reaction[8]—is ruled out[19] for the Cu(I)-catalyzed reaction on the basis of DFT calculations which show that reaction via a (formally Cu(III)) metallacycle is a more favorable pathway by up to 11.7 kcal mol^{-1} (Scheme 1).[5b,20,21] The same calculations suggest that the rate-determining step is the formation of the Cu metallacycle from a reactive intermediate involving copper-coordinated alkyne and, presumably, azide (organoazido−metal complexes are likely intermediates in many transition-metal-mediated reactions of azides, and Cu(I)−N$_3$R complexes have been characterized by X-ray crystallography[22]). However, the exact nature of this reactive intermediate is unclear (Scheme 1, types A−C).

In the absence of competing ligands,[23] copper(I) acetylides exist as complex multi metal atom aggregates,[24] and kinetic studies[17a,25] by Fokin and Finn on the generic ligand-free[23] Cu(I)-catalyzed alkyne−azide reaction show that in DMSO−water mixtures the reaction mechanism is second-order with respect to copper. The same studies found first-order kinetics with respect to the azide and alkyne (actually slightly higher than first-order with respect to the alkyne).[25] However, relatively little is known about the ligand-promoted Cu(I)-catalyzed cycloaddition in organic solvents. Recent experiments by Straub,[26] in which mononuclear copper(I) acetylides ligated to a sterically demanding *N*-heterocyclic carbene react efficiently with bulky organoazides at room temperature, support the notion that a single copper atom mechanism (A(i), Scheme 1) is viable for the reaction, at least when the copper is bound to bulky ligands. Recent DFT calculations[7c,21] suggest that π-activation of the copper acetylide unit by coordination of a second copper atom (e.g., A(ii) or, more likely under ligand-free conditions or with small monodentate ligands, bridged[27] intermediates such as B(i) or B(ii), Scheme 1) greatly enhances the reactivity of the copper σ-acetylide, accelerating formation of the metallacycle. Alternatively, a pathway[25] in which the reacting azide and alkyne are coordinated to different copper(I) atoms (intermediate C(i) or C(ii)) would also be consistent with the second-order kinetics observed in DMSO−water. It may well be that several of these types of intermediates[28] can provide viable pathways for the CuAAC reaction, with the different characteristics of the intermediates being relatively favored or inhibited by factors such as the solvent, bulk and coordination number of an added ligand, the strength of ligand−copper binding, and the amount of ligand-free Cu(I) present in solution. Given the tendency of copper(I) acetylides to aggregate, however, doubly bridged intermediates such as B or C should be abundant species under most conditions. Accordingly, if coordination of the azide to the same copper atom significantly increases the reactivity of the σ-acetylide, type B(ii) intermediates are probably involved in the dominant pathways in most reported CuAAC reactions.

Despite the uncertainty over the precise nature of the reactive intermediate, since tertiary amines and pyridines facilitate[5b,17] the reaction in organic solvents, we reasoned that a macrocycle, **1**, bearing an endotopic ligating nitrogen atom might be able to direct the CuAAC reaction of a "stoppered" alkyne, **2**, and a "stoppered" azide, **3**, through the macrocycle cavity to give a [2]rotaxane, **4**, in an active-metal template synthesis (Scheme 2).

Active-Metal Template CuAAC Rotaxane Synthesis

A 2,6-bis[(alkyloxy)methyl]pyridine macrocycle (**1a**), previously used[29] as both a mono- and bidentate ligand for various transition metals in classical "passive" template rotaxane and catenane syntheses, seemed a suitable candidate for initial investigations. Pleasingly, stirring of an equimolar mixture of

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[15] The Cu(I)-catalyzed terminal alkyne−azide cycloaddition is often referred to as the "Sharpless copper click reaction" or the "Sharpless−Huisgen alkyne−azide cycloaddition". However, Sharpless gives Fokin the credit for the idea and recognition of the copper catalysis of this reaction at Scripps [Rouhi, A. M. *Chem. Eng. News* **2004**, *82* (7), 63−65]. The initial work at Scripps was carried out shortly after, and without knowledge of, the first paper (ref 5a) describing the Cu(I)-catalyzed alkyne−azide cycloaddition (on solid-supported resins) had been submitted by Meldal and co-workers.

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[17] (a) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853−2855. (b) Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2004**, *126*, 9152−9153.

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[19] If the [2+3] cycloaddition were the preferred mechanism of the Cu-catalyzed reaction, the structures A−C shown in Scheme 1 would still be relevant as reactive intermediates.

[20] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210−216.

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[23] In this paper we use the phrases "ligandless" and "ligand-free" to describe copper that is not bound to the macrocyclic pyridine ligands added to the CuAAC reactions to generate the active-template synthesis. As discussed in the text and ref 28, any Cu(I) that is not coordinated to pyridine units will be complexed by molecules of acetonitrile, azide, alkyne, water, or other donor atoms present.

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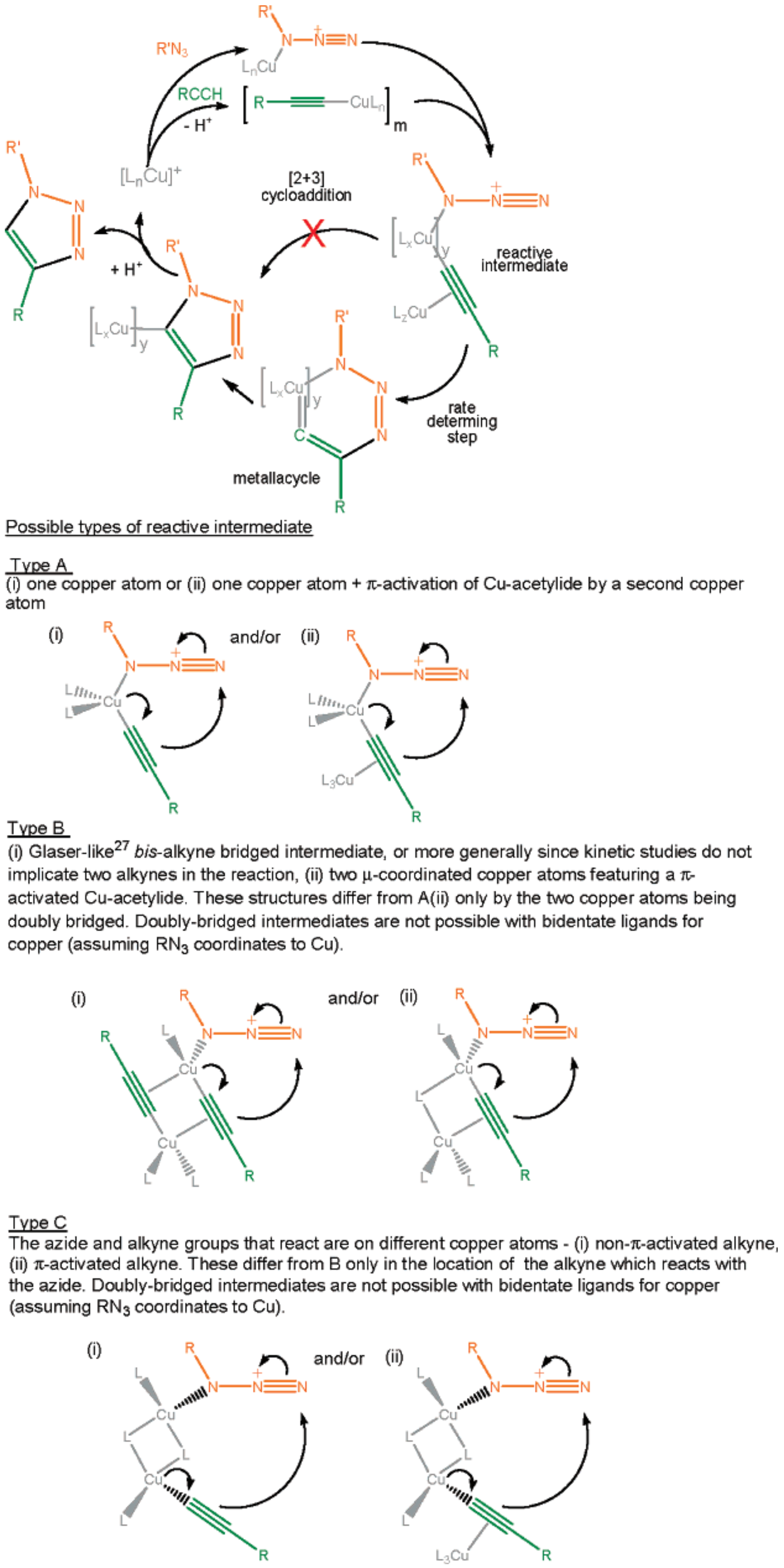
[28] Note: Copper(I) acetylides are generally complex extended multiatom aggregates, at least in the solid state and in the absence of good nitrogen ligands (see ref 24). The types of reactive intermediates shown in Scheme 1 are not meant to be precise or definitive structures—indeed, some of them (e.g., A(ii) and B(ii)) are very closely related—but rather are meant to illustrate different (possible) features of the putative reactive intermediate: How many copper atoms are needed to play significant structural or electronic roles during the catalysis? Is the copper σ-acetylide π-activated by an additional Cu atom? If the intermediate has two or more copper atoms, is it doubly bridged—as envisaged for a Glaser coupling, which can be ruled out with bidentate ligands for Cu if azide is also coordinated—or singly bridged? Are the reacting azide and alkyne attached to the same or different Cu atoms?

Scheme 1. Proposed Mechanism of the Huisgen−Meldal−Fokin Cu(I)-Catalyzed Alkyne−Azide Cycloaddition (CuAAC) Reaction[48]



Possible types of reactive intermediate

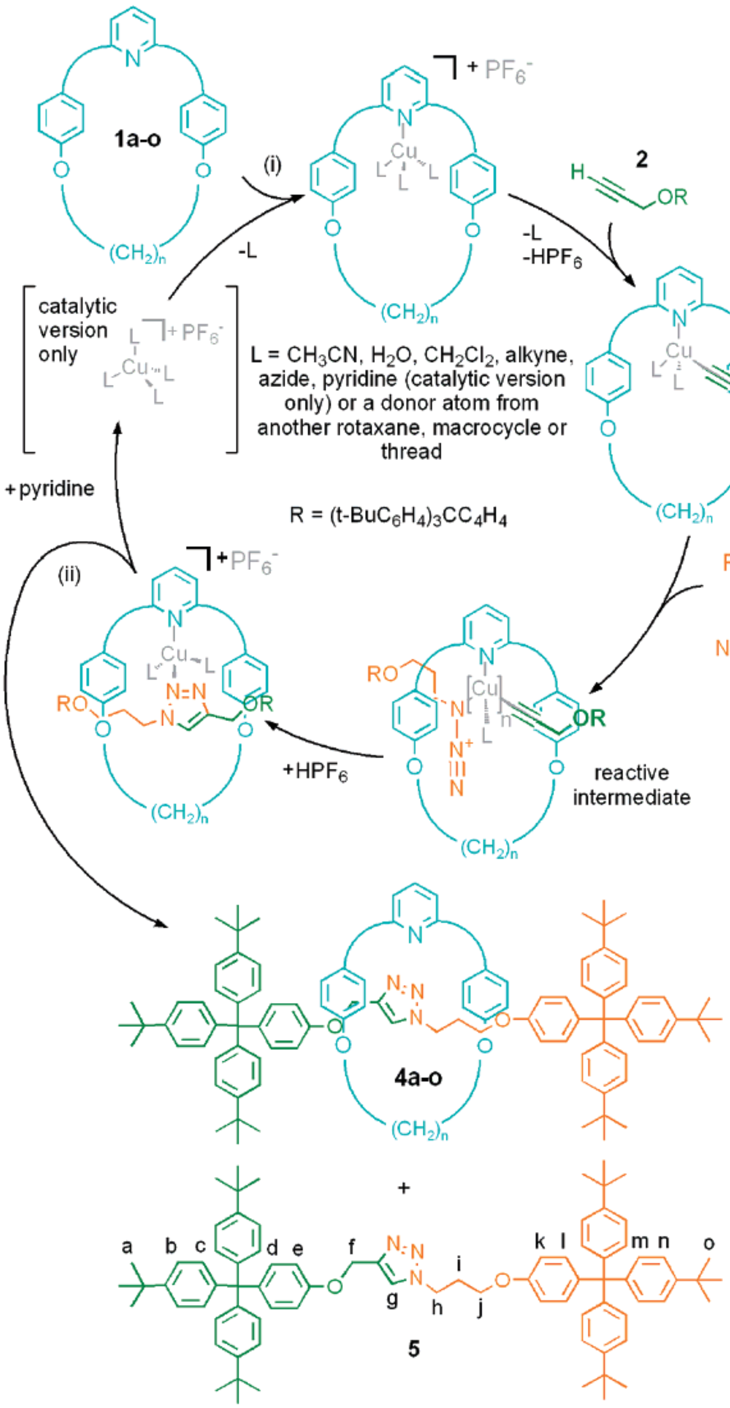
Type A
(i) one copper atom or (ii) one copper atom + π-activation of Cu-acetylide by a second copper atom

Type B
(i) Glaser-like[27] *bis*-alkyne bridged intermediate, or more generally since kinetic studies do not implicate two alkynes in the reaction, (ii) two μ-coordinated copper atoms featuring a π-activated Cu-acetylide. These structures differ from A(ii) only by the two copper atoms being doubly bridged. Doubly-bridged intermediates are not possible with bidentate ligands for copper (assuming RN$_3$ coordinates to Cu).

Type C
The azide and alkyne groups that react are on different copper atoms - (i) non-π-activated alkyne, (ii) π-activated alkyne. These differ from B only in the location of the alkyne which reacts with the azide. Doubly-bridged intermediates are not possible with bidentate ligands for copper (assuming RN$_3$ coordinates to Cu).

the pyridine macrocycle **1a**, alkyne **2**, azide **3**, and [Cu(CH$_3$CN)$_4$](PF$_6$) in CH$_2$Cl$_2$ for 24 h afforded—after demetalation with KCN—a mixture of [2]rotaxane **4a** (57%) and the noninterlocked triazole thread **5** (41%), together with some of the unconsumed starting macrocycle (Scheme 2 and Table 1, entry 1).[3] By varying the reaction conditions and reactant stoichiometry (Table 1), yields of up to 94% of [2]rotaxane with respect to the amount of macrocycle used were achieved (5 equiv of **2** and **3**; Table 1, entry 2) for this stoichiometric active-metal template reaction (Figure 1a). The use of substoichiometric amounts of copper was investigated to determine whether the metal would turn over as both a template and a cycloaddition catalyst (i.e., a

Scheme 2. Active-Metal Template CuAAC Synthesis of [2]Rotaxanes **4a**−**o** from Alkyne **2**, Azide **3**, and Macrocycles **1a**−**o**[a]



[a] Reagents and conditions: (i) **1a**−**o** (0.01 M), Cu(I) salt (generally $[Cu(CH_3CN)_4](PF_6)$; see the text), poorly coordinating solvent (generally CH_2Cl_2; see the text), and, in the catalytic version of the active-metal template reaction (Figure 1b), 3 equiv of pyridine; (ii) KCN, CH_2Cl_2/CH_3OH.[3] For the effect of the reaction conditions and reagent stoichiometry on the yields of **4a** and **5**, see Table 1. For the relative yields of **4a**−**o** using a standardized set of reaction conditions see Figure 4
.

catalytic active-metal template synthesis, Figure 1b). When using 20 mol % (with respect to **1a**) $[Cu(CH_3CN)_4](PF_6)$ at room temperature, the reaction appeared to stop after an amount of [2]rotaxane equivalent to the amount of copper present had been formed, suggesting that the multidentate rotaxane sequesters the transition metal during the reaction, inhibiting further catalytic activity. Addition of pyridine as a competing ligand enabled the catalyst to turn over, producing a substoichiometric reaction, but the reaction was extremely slow at 25 °C (Table 1, entry 3). Elevating the temperature (70 °C, $ClCH_2CH_2Cl$) gave an

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(29) (a) Fuller, A.-M.; Leigh, D. A.; Lusby, P. J.; Oswald, I. D. H.; Parsons, S.; Walker, D. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3914−3918. (b) Fuller, A.-M. L.; Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z.; Walker, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 12612−12619. (c) Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z.; Walker, D. B. *Chem. Commun.* **2005**, 4919−4921. (d) Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z.; Walker, D. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 4557−4564. (e) Fuller, A.-M. L.; Leigh, D. A.; Lusby, P. J. *Angew. Chem., Int. Ed*. **2007**, *46*, 5015−5019.

Table 1. Effect of Reaction Conditions and Reagent Stoichiometry on the Active-Metal Template CuAAC Synthesis of [2]Rotaxane **4a** (Scheme 2)[3]

entry	amt of **2** and **3** (equiv)	amt of $[Cu(CH_3CN)_4](PF_6)$ (equiv)	solvent	*T* (°C)	conversion to triazole **2** + **3** → **4a** + **5** (%)	yield of rotaxane **1a** → **4a** (%)
1[a]	1	1	CH_2Cl_2	25[d]	>95	57
2[a]	5	1	CH_2Cl_2	25[d]	92	94
3[b]	5	0.2	CH_2Cl_2	25[d]	44	59
4[b]	5	0.2	$ClCH_2CH_2Cl$	25 → 70[e]	94	82
5[c]	1	0	$ClCH_2CH_2Cl$	25 → 70[f]	<5	0

[a] All reactions were carried out at 0.01 M concentration with respect to **1a** using the procedure shown in Scheme 2. [b] 3 equiv of pyridine. [c] Control experiment with no $[Cu(CH_3CN)_4](PF_6)$ present to demonstrate that the thermal reaction does not occur at these temperatures. [d] 24 h. [e] 12 h and then 24 h. [f] 12 h and then 72 h.

improved yield (82%) of rotaxane **4a** in a reasonable time period (36 h) using only 4 mol % Cu(I) with respect to both **2** and **3** (Table 1, entry 4).

Effect of the Nature of the Cu(I) Source

A number of different Cu(I) salts were screened for the reaction shown in Scheme 2 using the conditions shown in Table 1, entry 1, but replacing the $[Cu(CH_3CN)_4](PF_6)$ salt with other Cu(I) complexes. The use of CuOTf•benzene gave a 78% conversion of **2** and **3** into triazole products after 24 h but only a 46% yield of [2]rotaxane **4a**. By letting the reaction continue for a further 2 days (72 h in total), complete conversion of the starting azide and alkyne to triazole products was achieved (48% rotaxane). Substituting CuI for $[Cu(CH_3CN)_4](PF_6)$ led to very little reaction during the first 24 h (8% conversion to triazole), presumably due to the low solubility of CuI in CH_2Cl_2, but interestingly, what little alkyne and azide had reacted formed rotaxane with high selectivity (7:1 rotaxane:thread). The reaction proceeded slowly to completion (>98% conversion) over three weeks. However, at the end point of the reaction the product ratio (56:44 rotaxane:thread) was no different from that of the analogous $[Cu(CH_3CN)_4](PF_6)$-mediated experiment.

We also synthesized and isolated various discrete Cu(I)−**1a** complexes and tested their efficacy in the active-metal template reaction. The macrocycle **1a** and the different Cu(I) salts were mixed in CH_3CN solution and the resulting Cu(I)−**1a** complexes obtained through precipitation by vapor diffusion with diethyl ether. The preformed Cu(I)−**1a** complexes were submitted to the standard rotaxane-forming reaction conditions (Table 1, entry 1). The preformed $[Cu(CH_3CN)_4](PF_6)$−**1a** complex gave 76% conversion to triazole and a 53% yield of [2]rotaxane; the preformed CuOTf−**1a** complex gave 53% conversion to triazole but only a 5% yield of [2]rotaxane; the preformed CuI−**1a** complex gave results identical to those of the CuI−**1a** complex formed in situ (i.e., >98% triazole conversion over 3 weeks, 56% rotaxane).

Although there is some variation in the efficacy of the various Cu(I) salts on the rotaxane-forming reaction and some unexplained variation in the rotaxane:thread ratio during the course of the reaction with some sources of Cu(I), simple addition of $[Cu(CH_3CN)_4](PF_6)$ is the most convenient way of maximizing the CuAAC yield of rotaxane.[30]

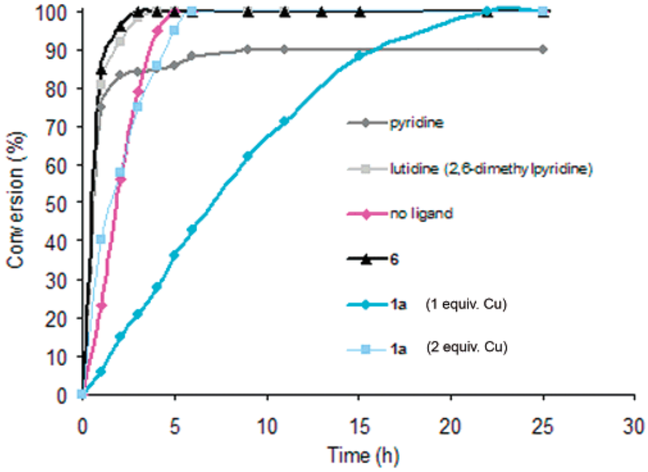

Figure 2. Conversion to triazole (i.e., thread + rotaxane if applicable) vs time for different pyridine-based ligands for the CuAAC reaction. Conditions: (i) ligand (1 equiv), alkyne **2** (1 equiv), azide **3** (1 equiv), $[Cu(CH_3CN)_4](PF_6)$ (1 equiv, 1 or 2 equiv with **1a**), CD_2Cl_2, rt, 0.01 M. The conversion of **2** and **3** into the triazole products (thread **5**, + rotaxane **4a** where relevant) was monitored by ^1H NMR.

Kinetic Studies

Some simple kinetic measurements were made to determine whether, under these reaction conditions, the Cu(I)-catalyzed alkyne−azide cycloaddition is actually accelerated by pyridine-based ligands. The rate of formation of triazole products (i.e., thread, plus rotaxane where relevant) was compared for the ligand-free[23] reaction and reactions containing pyridine, 2,6-dimethylpyridine (lutidine), 2,6-bis[(alkyloxy)methyl]pyridine macrocycle **1a**, and **6**, a close but acyclic analogue of **1a**.

The results (Figure 2) show that both lutidine and **6**, the acyclic analogue of **1a**, significantly accelerate the CuAAC reaction rate (essentially complete conversion to triazole after 3 h) compared to that of the Cu(I)-catalyzed reaction when no pyridine-based ligand is added (complete conversion after 6 h). The presence of pyridine also initially accelerates the reaction, but the conversion tails off after 2 h, suggesting that using unsubstituted pyridine as a ligand facilitates the oxidation of Cu(I) to noncatalytic Cu(II) under the reaction conditions. The role of the pyridine ligands in the rate acceleration is probably to break up extended copper(I) acetylide aggregates to form smaller reactive intermediates of the types shown in Scheme 1, although we cannot rule out an electronic effect of the ligand on the metal as well.

Interestingly, the Cu(I)-catalyzed formation of triazole products (both rotaxane and thread) in the presence of macrocycle **1a** (with 1 equiv of Cu)—which also presumably breaks up the

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(30) We also examined the effect of different alkyne substrates on the rotaxane formation. The alkynes (see the Supporting Information) were submitted to the standard click reaction conditions (Scheme 2). Using a longer, more flexible, alkylalkyne or an arylalkyne in the place of **2** led to similar yields of the corresponding [2]rotaxanes (and similar overall conversions of the substrates into triazole products), indicating the active-metal template rotaxane-forming reaction is rather insensitive to substrate modifications.

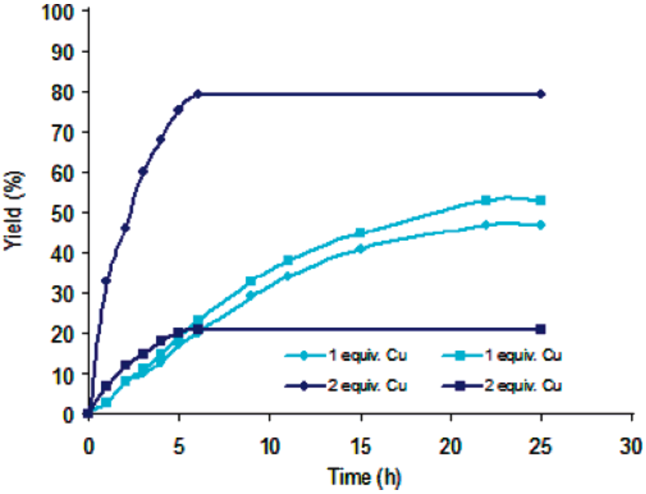

Figure 3. Formation of triazole products (rotaxane **4a,** ■; thread **5**, ●) vs time for the CuAAC reaction in the presence of macrocycle **1a**. Conditions: (i) **1a** (1 equiv), **2** (1 equiv), **3** (1 equiv), [Cu(CH_3CN)$_4$](PF_6) (1 or 2 equiv), CD_2Cl_2, rt, 0.01 M. The conversion of **2** and **3** into thread **5** and rotaxane **4a** was monitored by ^{1}H NMR.

copper acetylide aggregates—is actually *slower* (24 h compared to 6 h) than the ligand-free Cu(I)-catalyzed reaction. While it might seem surprising that the active-metal template reaction is slower than the ligand-free reaction given that excellent yields of rotaxane are obtained under both stoichiometric and catalytic active-metal template conditions (Table 1), the rationale for this is quite straightforward. First, the alkyne−azide cycloaddition with the macrocyclic ligand must take place *through* the macrocycle cavity, a sterically restricted environment compared to the ligandless Cu(I)-catalyzed reaction, effecting the solvation of the reactive species as well as hindering any motion required to achieve bond formation or changes of geometry at the copper center. Second, the macrocyclic ligand might disfavor certain types of reactive intermediates (e.g., B) on steric grounds, so the reaction may proceed through another type of slower reacting, but still viable, intermediate (e.g., A or C rather than B). The reason that the ligandless formation of the triazole thread does not dominate given the slow rate of rotaxane formation is that the macrocycle is an excellent ligand for the Cu(I) and sequesters it, preventing the inherently faster ligand-free reaction (probably via B(ii)) from occurring. Accordingly, addition of a second equivalent of Cu(I) to the reaction containing **1a** should accelerate the rate of triazole formation to close to the ligand-free rate. Indeed, this was found to be the case (Figures 2 and 3). However, while one might expect this increase to be totally due to thread formation, analysis shows that the rate of *rotaxane* formation is also increased by adding an extra equivalent of Cu(I) to this reaction (Figure 3). In fact, the final yield of [2]-rotaxane only falls from 57% to 22% even though the triazole-forming reaction is complete in 6 h instead of 24 h. The acceleration of the rotaxane-forming reaction by excess Cu(I) strongly suggests that π-activation of the copper acetylide unit (see Scheme 1) is the dominant process in the CuAAC reaction mechanism of **1a**.

Effect of the Macrocycle Structure on [2]Rotaxane Formation

To further investigate both the scope and the mechanism of the active-template rotaxane-forming reaction shown in Scheme 2, we varied the structure of the pyridine-based macrocycle. The macrocycles used in the study are shown in Figure 4, and their syntheses are detailed in the Supporting Information. To compare the relative yields of rotaxane and thread within the ligand series, the macrocyclic ligands were screened using a standard, rather than optimized,[31] set of stoichiometric active-metal template reaction conditions in which the original macrocycle **1a** generates appreciable quantities of both rotaxane and thread. The conditions used were 1 equiv of macrocycles **1a**−**o**, 1 equiv of alkyne **2**, 1 equiv of azide **3**, and 1 equiv of [Cu(CH_3CN)$_4$](PF_6) at a concentration of 0.01 M in CH_2Cl_2 at room temperature for 24 h. In most cases the starting alkyne **2** and azide **3** were completely consumed during the course of the reaction. After 24 h (72 h for **1n** and **1o**) each reaction was treated with KCN to remove the Cu(I), analyzed by ^{1}H NMR to determine the yield (shown in Figure 4) under the standard set of conditions, and then purified to give authentic samples of each [2]rotaxane. The yield (the percentage shown in red in Figure 4) of each rotaxane is the conversion of the macrocycles **1a**−**o** to the corresponding [2]rotaxanes **4a**−**o**. The conversion to triazole (the percentage shown in parentheses in Figure 4) is the overall conversion of the alkyne **2** and azide **3** into both thread **5** and rotaxanes **4a**−**o**.

Mono- and Tridentate Macrocycles. In addition to the strongly coordinating pyridine nitrogen, macrocycle **1a** has two ether oxygen atoms that could potentially be involved in (albeit weak) coordination to the metal atom during the active-template reaction, making **1a** a monodentate or possibly weakly bidentate or very weakly tridentate ligand.[32] Not only is macrocycle **1b** missing the ether oxygen atoms, but the pyridine nitrogen atom lone pair is tied up in strong intramolecular bifurcated hydrogen bonds to the adjacent amide groups,[33] so it was rather surprising to find that [2]rotaxane **4b** was successfully produced in the active-metal template reaction, albeit in only 6% yield. Coordination of **1b** to the copper occurs at the expense of the intramolecular hydrogen bonds[34,35] so that **1b** is able to act as an effective monodentate ligand. In contrast, the use of **1c**—a tridentate macrocyclic ligand with three hard donor atoms—gave a similar overall conversion to triazole but with no rotaxane

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(31) The standard reaction conditions use 1 equiv of each reagent and low temperatures to minimize the background uncatalyzed thermal cycloaddition. These conditions were chosen to allow the relative efficacy of the different macrocycles in promoting rotaxane formation to be assessed. No attempt was made to optimize the reaction conditions to improve the rotaxane yields reported in Figure 4. For macrocycles **1a**, **1i**, **1j**, **1f**, **1l**, **1m**, and **1n**—all of which produce significant rotaxane and are not degraded under the reaction conditions—virtually all the macrocyclic ligand can be converted to rotaxane by using extended reaction times and an excess of the azide and alkyne building blocks.

(32) For an X-ray structure of **1a** as a monodentate ligand in a rotaxane (Pd(II) as the metal atom) see ref 29b; for X-ray structures of a related pyridine diether ligand acting as a bidentate ligand in a rotaxane (Cu(II) or Ni(II) as the metal atom) see ref 29d.

(33) (a) Hunter, C. A.; Purvis, D. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 792−795. (b) Johnston, A. G.; Leigh, D. A.; Nezhat, L.; Smart, J. P.; Deegan, M. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1212−1216. (c) Leigh, D. A.; Moody, K.; Smart, J. P.; Watson, K. J.; Slawin, A. M. Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 306−310. (d) Leigh, D. A.; Murphy, A.; Smart, J. P.; Slawin, A. M. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 728−732. (e) Leigh, D. A.; Murphy, A.; Smart, J. P.; Deleuze, M. S.; Zerbetto, F. *J. Am. Chem. Soc.* **1998**, *120*, 6458−6467. (f) Deleuze, M. S.; Leigh, D. A.; Zerbetto, F. *J. Am. Chem. Soc.* **1999**, *121*, 2364−2379. (g) Clegg, W.; Gimenez-Saiz, C.; Leigh, D. A.; Murphy, A.; Slawin, A. M. Z.; Teat, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4124−4129. (h) Biscarini, F.; Cavallini, M.; Leigh, D. A.; León, S.; Teat, S. J.; Wong, J. K. Y.; Zerbetto, F. *J. Am. Chem. Soc.* **2002**, *124*, 225−233. (i) Bottari, G.; Dehez, F.; Leigh, D. A.; Nash, P. J.; Pérez, E. M.; Wong, J. K. Y.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5886−5889. (j) Leigh, D. A.; Venturini, A.; Wilson, A. J.; Wong, J. K. Y.; Zerbetto, F. *Chem.*—*Eur. J.* **2004**, *10*, 4960−4969.

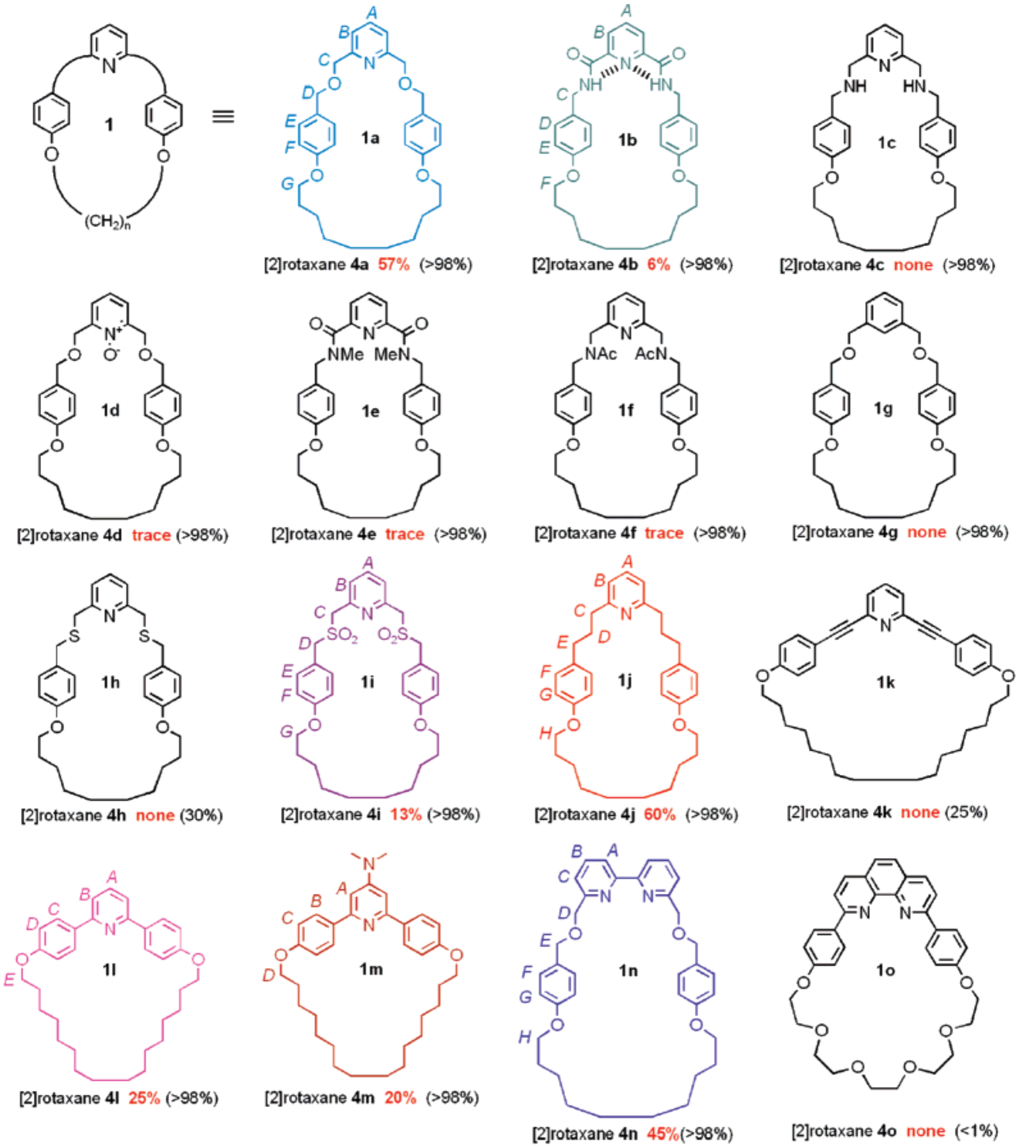

Figure 4. Influence of the macrocycle structure on the active-metal template CuAAC rotaxane-forming reaction in Scheme 2 under a standardized set of reaction conditions. Conditions for Scheme 2: (i) **1a**−**o**, **2**, **3**, $[Cu(CH_3CN)_4](PF_6)$, CH_2Cl_2, rt, 24 h (72 h for **4n** and **4o**), 0.01 M concentration with respect to each of **1a**−**o**, alkyne **2**, azide **3**, and $[Cu(CH_3CN)_4](PF_6)$; the reactions were not run under an inert atmosphere, nor using distilled or dried solvents; (ii) KCN, CH_2Cl_2/CH_3OH. The conversion of each macrocycle to [2]rotaxane is given as a percentage yield in red, and the overall conversion of **2** and **3** into triazole products (rotaxanes **4a**−**o** and thread **5**) is shown for each macrocycle in parentheses. The designation "trace" means that the rotaxane was observed by ESI-MS but could not be detected by ^{1}H NMR. The colors and lettering correspond to the signals and assignments of the ^{1}H NMR spectra shown in Figure 5.

formed. Upon addition of **1c** to the copper catalyst and other reagents the solution changed color immediately from colorless to blue-green. This suggests that most of the Cu(I) is rapidly oxidized to Cu(II) upon coordination to **1c**.[36] The resulting Cu(II)−**1c** complex is not catalytically active for the alkyne−azide cycloaddition, and any tridentate Cu(I)−**1c** complex lacks the free coordination sites necessary to bind azide and alkyne in the same aggregate.[37] However, enough of the copper in the reaction is not tied up as the **1c** complex for the ligandless thread-forming triazole reaction to proceed to completion within 24 h.

Macrocycle **1d** has a structure similar to that of **1a** except that the pyridine nitrogen is oxidized. The result, >98% conversion to triazole but only a trace of rotaxane when using **1d** as the macrocycle in the active-template reaction, shows that the *N*-oxygen atom greatly affects the ligand's ability to coordinate to Cu(I). Macrocycle **1e** also has a constitution

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(34) Hydrogen bond energies are usually in the range of 1−10 kcal/mol, whereas coordinate bonds have energies of 20−80 kcal/mol;[35] thus, the stabilization of the copper(I) ion upon coordination should compensate for the loss of the two hydrogen bond interactions. In fact, all of the pyridine-containing macrocycles studied exhibit complexation-induced shifts in the ^{1}H NMR spectra ($CDCl_3$) upon addition of $[Cu(CH_3CN)_4](PF_6)$, indicating that copper(I) ions interact with the macrocycles in every case.

(35) Goshe, A. J.; Crowley, J. D.; Bosnich, B. *Helv. Chim. Acta* **2001**, *84*, 2971−2985.

(36) This oxidation of Cu(I) to Cu(II) in the presence of **1c** occurs even when great care is taken to exclude both moisture and oxygen from the reaction mixture. It appears that the macrocycle itself is the oxidant. However, there is some remaining $[Cu(CH_3CN)_4](PF_6)$ which catalyzes the formation of the thread **5**.

(37) The multidentate ligand tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) is a highly effective copper ligand for the CuAAC reaction [see refs 6b and 17a,b and Gupta, S. S.; Kuzelka, J.; Singh, P.; Lewis, W. G.; Manchester, M.; Finn, M. G. *Bioconjugate Chem.* **2005**, *16*, 1572−1579]. However, the individual triazole-functionalized "arms" of TBTA are weakly coordinating ligands, so TBTA probably functions by the alkyne and azide displacing two of the triazole groups to form the reactive intermediate.

similar to that of **1b**, but the secondary amides are methylated, eliminating their ability to form hydrogen bonds. AM1 calculations[38,39] using Spartan (see the Supporting Information) show that the methyl groups distort and partially fill the macrocycle cavity. The result is that, like that of **1d**, little of the CuAAC reaction is directed through the macrocycle cavity to form rotaxane. The same effect is seen for macrocycle **1f**, the bis-*N*-acetylated analogue of **1c**.

Removing the pyridine nitrogen atom, macrocycle **1g**, completely switches off rotaxane formation, confirming the need for a ligating donor atom. Replacing the benzylic oxygens of **1a** by more strongly coordinating sulfur atoms produces another tridentate macrocycle, **1h**. As with **1c**, no rotaxane is formed—consistent with the premise that tridentate ligand complexes of Cu(I) lack the vacant coordination sites necessary to bind both azide and alkyne[37]—and the yield of triazole is also only 30%, indicating that **1h** is particularly effective in sequestering the copper. Oxidation of the sulfide groups to sulfones, macrocycle **1i**, restores the ability of the macrocycle to bind to the Cu(I) as a monodentate ligand, and despite the increased bulk around the coordinated metal ion, a significant amount (13%) of [2]-rotaxane **4i** is formed by the stoichiometric active-metal template reaction. In fact, substitution of the benzylic ether oxygen atoms by methylene groups confirms that only a monodentate macrocycle with a single strongly coordinating donor atom is required for an efficient active-template rotaxane-forming reaction; macrocycle **1j** generates just as much [2]rotaxane as the parent macrocycle **1a**. Modeling suggests that the cavity of macrocycle **1j** is rather more flexible than that of **1a**, yet this is not detrimental for rotaxane formation.

To test whether other macrocycle geometries would be tolerated by the active-template reaction, we prepared **1k** and **1l** in which the substituted benzylic units were replaced by arylalkynyl and aryl groups, respectively. The 2,6-bisalkynylpyridine unit proved to be unstable[40,41] under the reaction conditions, suppressing the overall yield of the CuAAC reaction, with no rotaxane being produced. However, the active-metal template CuAAC reaction proceeded smoothly with **1l**, albeit generating rather less rotaxane (25%) than the most effective examples of other macrocycle geometries (**1a** and **1j**). AM1 calculations[38] using Spartan (see the Supporting Information) indicate that **1l** has a well-defined persistent cavity suitable for the threading of a molecular chain. However, the phenyl groups flanking the pyridine sterically encumber the nitrogen donor atom of the macrocycle, and a combination of steric and electronic factors probably reduces the binding strength of this macrocycle for Cu(I) ions. The weaker binding leads to more ligandless[23] Cu(I) in solution, resulting in higher conversion of the substrates into the noninterlocked thread **5** and the relatively modest yield of [2]rotaxane **4l**. Increasing the steric bulk at the 4-position of the pyridine group while simultaneously increasing the electron-donating ability of the heterocyclic nitrogen atom, macrocycle **1m**, had little effect on the rotaxane yield.

Bidentate Macrocycles. Having established that monodentate ligands of several different macrocycle geometries and donor atom orientations (**1a**, **1j**, **1l**, **1m**) efficiently promote active-template rotaxane formation, whereas strongly tridentate macrocycles (**1c** and **1h**) do not, we investigated the efficacy of bidentate macrocycles **1n** and **1o**.[17,42] The bipyridyl macrocycle **1n** directs the CuAAC reaction through its cavity to form rotaxane almost as efficiently as the best monodentate macrocycles (45% for **1n** → **4n** compared to 57% for **1a** → **4a** and 60% for **1j** → **4j**). However, it severely inhibits the rate of the Cu(I)-catalyzed reaction, and it took 3 days for the active-metal template reaction **1n** → **4n** to go to completion, compared to 24 h for **1a** → **4a** and 6 h for the ligand-free Cu(I)-catalyzed control reaction (Figure 3). The inhibition of the Cu(I)-catalyzed cycloaddition is even more dramatic with the other bidentate ligand investigated, the 2,9-diphenylphenanthroline macrocycle **1o** used extensively to assemble rotaxanes and catenanes by the Sauvage group.[1b,i] Macrocycle **1o** completely inhibits the CuAAC reaction. Even after 3 days under the standard stoichiometric active-metal reaction conditions in the presence of **1o**, no triazole products were observed. This latter result is particularly interesting given that phenanthroline ligands have previously been reported[17] to promote the CuAAC reaction. The lack of reactivity is presumably a result of the steric bulk about the Cu(I) center in the complex preventing the complex from undergoing the various structural variations required for reaction to take place (e.g., tolerating the change in geometry from Cu(I) to the formal Cu(III) species, Scheme 1), together with the macrocycle being very effective in sequestering the Cu(I) in this unreactive form. A related Cu(I)−macrocycle complex has recently been reported to promote the formation of [2]rotaxanes via a Glaser alkyne homocoupling.[13] However, in that case, intermediates of type B (Scheme 1) are possible with a bidentate ligand for copper because no azide need be coordinated to the metal atom.

^{1}H NMR Spectra of the Metal-Free [2]Rotaxanes

The ^{1}H NMR spectra (400 MHz, 300 K, $CDCl_3$) for each of the rotaxanes formed in >5% yield are shown in Figure 5. The ^{1}H NMR spectra of the rotaxanes (Figure 5b−g) all show upfield shifts of several signals with respect to the signals of the noninterlocked components (thread **5**, Figure 5a, and the macrocycles **1a**, **1b**, **1i**, **1j**, **1m**, and **1n**; see the Supporting Information). Such shielding is typical of interlocked structures in which the aromatic rings of one component are positioned face on to with another component and is observed for all the nonstopper resonances of the axle (H_{f-j}), indicating that the macrocycle accesses the full length of the thread. This is as expected; there should be no strong intercomponent noncovalent interactions between the thread and the macrocycle in the metal-free rotaxanes. The one exception is the amide-containing rotaxane **4b** (Figure 5c), which exhibits a significant downfield shift of the amide resonance with respect to that of the free macrocycle (see Supporting Information). This can be attributed to hydrogen bonding between the amides of the macrocycle and

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(38) Minimum energy conformations were calculated for each of the metal-free macrocycles using the Spartan molecular modeling program (Semi-Empirical, AM1). The results are provided in the Supporting Information.

(39) In the case of **1e** no hydrogen bonds are present, thus allowing the Cu(I) ion better access to the macrocycle's pyridine nitrogen atom. However, in each of macrocycles **1e** and **1f** the nitrogen atom of the pyridine is more hindered, which may reduce the binding ability of the ligand.

(40) Internal alkynes have been found to react under CuAAC conditions; see: Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.*—*Eur. J.* **2006**, *12*, 7558−7564.

(41) Macrocycle **1k** is also photosensitive and decomposes slowly in ambient light.

(42) Bidentate bipyridine and phenanthroline ligands have been shown to significantly enhance the kinetics of the CuAAC reaction; see ref 17b.

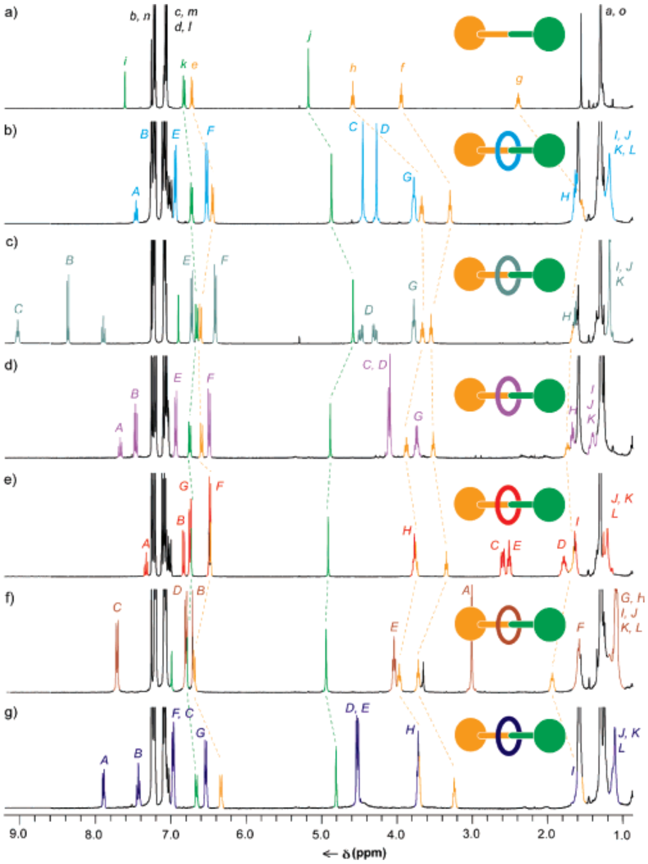

Figure 5. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) triazole thread **5**, (b) [2]rotaxane **4a**, (c) [2]rotaxane **4b**, (d) [2]rotaxane **4i**, (e) [2]rotaxane **4j**, (f) [2]rotaxane **4m**, and (g) [2]rotaxane **4n**. The assignments correspond to the lettering shown in Scheme 2 and Figure 4.

the triazole unit of the thread in an interaction similar to that previously observed between interlocked amide and pyridine components in rotaxanes and catenanes.[1j,29]

Active-Metal Template CuAAC Reaction at High Macrocycle:Cu(I) Ratios: Unexpected Formation of [3]Rotaxanes

The picture of the active-metal template CuAAC reaction that we can build up that is consistent with the experimental observations so far is that the ligand-free $[Cu(CH_3CN)_4](PF_6)$ salt and macrocycles **1a**−**o** are in equilibrium with the corresponding copper(I)−macrocycle complex in which, in most cases, the metal atom directs the cycloaddition of the azide and alkyne through the macrocycle cavity. Although the ligand-free reaction is inherently faster than the active-metal template one, the coordinating ability of the macrocycle means that the rotaxane-forming reaction can become competitive with, or even dominate, the thread-forming reaction. In general, a stronger binding macrocyclic ligand (e.g., **1a** compared to **1b**) should move this equilibrium in favor of rotaxane formation. However, some changes in coordination geometry about the metal are required for the CuAAC mechanism to operate (Scheme 1), so the most strongly binding macrocycle (**1o**), which apparently does not tolerate such changes, actually inhibits the rotaxane-forming reaction. In view of this, we decided to investigate other conditions in which rotaxane formation might be increased at the expense of the thread.

In an attempt to minimize the amount of ligandless Cu(I) present in the reaction, we carried out the active-metal template CuAAC protocol under the standard set of conditions (1 equiv of **2**, 1 equiv of **3**, 1 equiv of $[Cu(CH_3CN)_4](PF_6)$, CH_2Cl_2, rt) used previously but in the presence of 10 equiv of macrocycle (Scheme 3). Our initial experiments[43] were carried out with monodentate macrocycle **1l**, and we were immediately intrigued to find that the reaction was much slower with 10 equiv of the macrocycle than it had been with 1 equiv, the higher macrocycle:Cu(I) reaction taking more than one week to go to completion. Upon reaching this end point, the mixture of triazole products was found to consist of 30% thread **5**, 37% [2]rotaxane **4l**, and, to our surprise, 33% [3]rotaxane **7l** (yields quoted with respect to the alkyne and azide reactants). A reaction using macrocycle **1a** under the same experimental conditions (1 equiv of **2**, 1 equiv of **3**, 1 equiv of $[Cu(CH_3CN)_4](PF_6)$, and 10 equiv of **1a**, CH_2Cl_2, rt) was again slower than the same reaction with 1 equiv of macrocycle (3 days to reach completion compared to 24 h), generating a product mixture of 5% thread **5**, 90% [2]rotaxane **4a**, and 5% [3]rotaxane **7a** (yields quoted with respect to the alkyne and azide reactants). A similar but less dramatic trend was seen with bidentate macrocycle **1n**; with 10 equiv of **1n** the reaction took 10 days to complete (cf. 3 days with 1 equiv), producing 3% thread **5** and 97% [2]rotaxane **4n** (in this case no [3]rotaxane **7n** could be detected by ^{1}H NMR spectroscopy).

The remarkable features of these high macrocycle:Cu(I) ratio active-metal template reactions are the following:

(i) Exceptional combined rotaxane yields: 95% ([2]rotaxane **4a** + [3]rotaxane **7a**) compared to 57% for **4a** with 1 equiv of **1a**; 70% ([2]rotaxane **4l** + [3]rotaxane **7l**) compared to 25% for **4l** with 1 equiv of **1l**; 97% ([2]rotaxane **4n**) compared to 45% for **4n** with 1 equiv of **1n**.

(ii) Significant slowing of the reaction rates compared to the low macrocycle:Cu(I) ratio reactions. The largest effect on the rate is seen with the weakly copper-binding macrocycle **1l**; the smallest effect on the rate occurs for the strongly copper-binding macrocycle **1n**. Again, this is strongly suggestive experimental evidence that the dominant mechanism of the CuAAC reaction under these conditions involves activation of the copper σ-acetylide unit by a second, preferably ligandless for steric reasons, copper atom (i.e., **I** or **II**, Scheme 3).

(iii) Formation of [3]rotaxane (in 33% yield using macrocycle **1l**)—i.e., *two* macrocycles being threaded during the formation of *one* triazole ring. Molecular models show that this can most reasonably occur through the sort of bridged two copper atom intermediate **III** shown in Scheme 3. Since such a doubly bridged intermediate cannot occur with bidentate ligands (and no [3]rotaxane is observed with **1n**), it seems likely that monodentate pyridine ligand-promoted CuAAC reactions proceed via doubly bridged intermediates such as **I** (Scheme 3), the equivalent of intermediate B(ii) in Scheme 1, whereas bidentate bipyridyl ligand-promoted CuAAC reactions proceed

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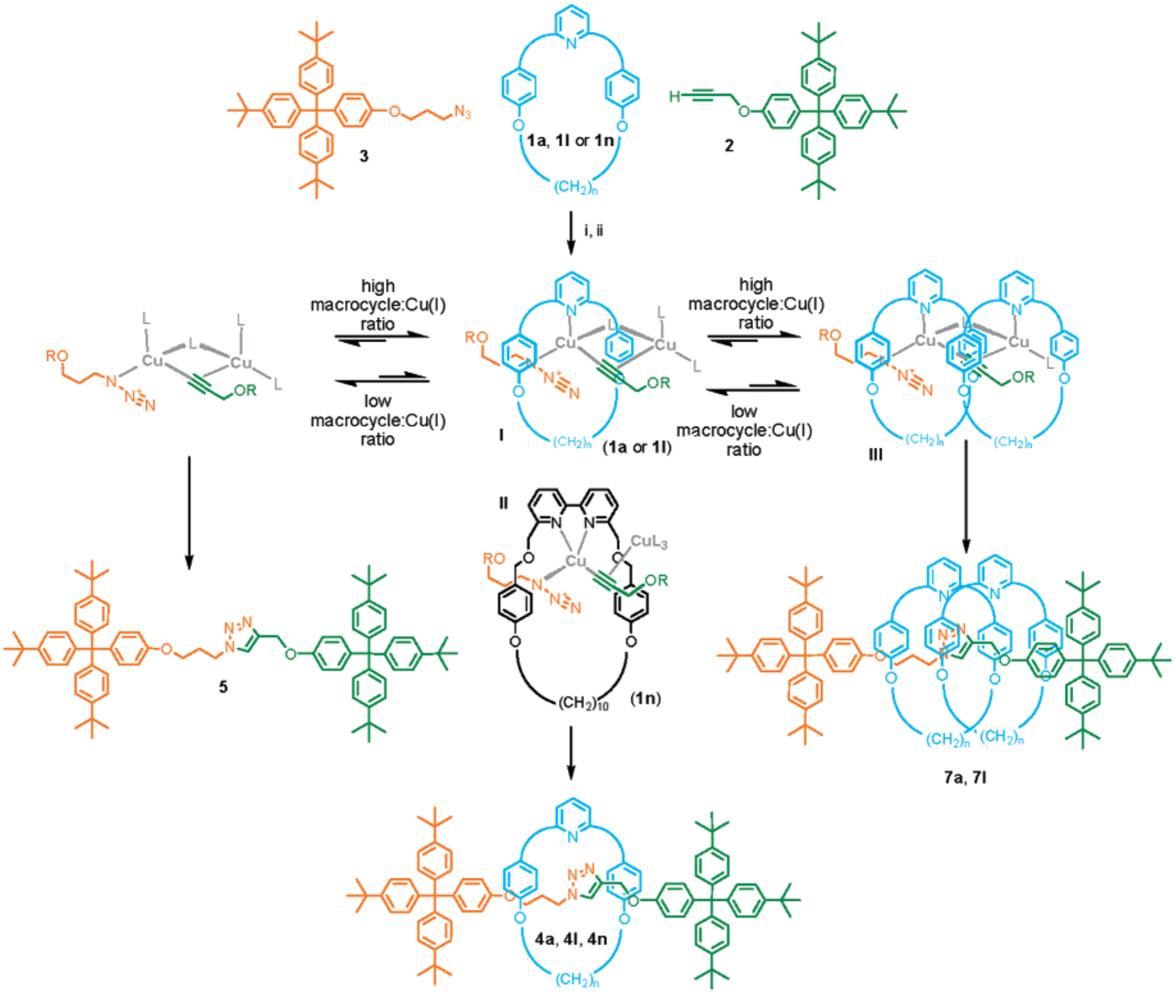
[43] We chose macrocycle **1l** for this study because it is a rather poor ligand (indeed, we were unable to generate complexes with it using several other metals) due to the steric crowding around the pyridine nitrogen and the π-electron density presented to the low-oxidation-state copper from the adjacent aromatic rings. The rather weak Cu(I) binding affinity—meaning there is more ligandless[23] Cu(I) present in solution than many of the other macrocycles shown in Figure 4—is most likely the reason for the modest yield of rotaxane using 1 equiv of this macrocycle. We reasoned the yield should be improved by increasing the macrocycle:copper ratio.

Scheme 3. Effect of the Macrocycle:Cu(I) Ratio on the Active-Metal Template CuAAC Reaction[a,b]



[a] Reagents and conditions: (i) **1a**, **1l**, or **1n** (10 equiv), **2** (1 equiv), **3** (1 equiv), $[Cu(CH_3CN)_4](PF_6)$ (1 equiv), CH_2Cl_2, rt, 24 h (**1a**), 7 days (**1l**), 10 days (**1n**); (ii) KCN, CH_2Cl_2/CH_3OH. Product yields starting from macrocycle **1a**: thread **5** (5%), [2]rotaxane **4a** (90%), [3]rotaxane **7a** (5%). Product yields starting from macrocycle **1a**: thread **5** (5%), [2]rotaxane **4i** (33%), [3]rotaxane **7l** (37%). Product yields starting from macrocycle **1n**: thread **5** (3%), [2]rotaxane **4n** (97%), [3]rotaxane **7n** (0%). [b]In the reactive intermediates shown, the copper azide (orange) reacts with any of the copper alkyne units shown in green. L can be any nonreacting ligand, including other alkyne and azide groups.

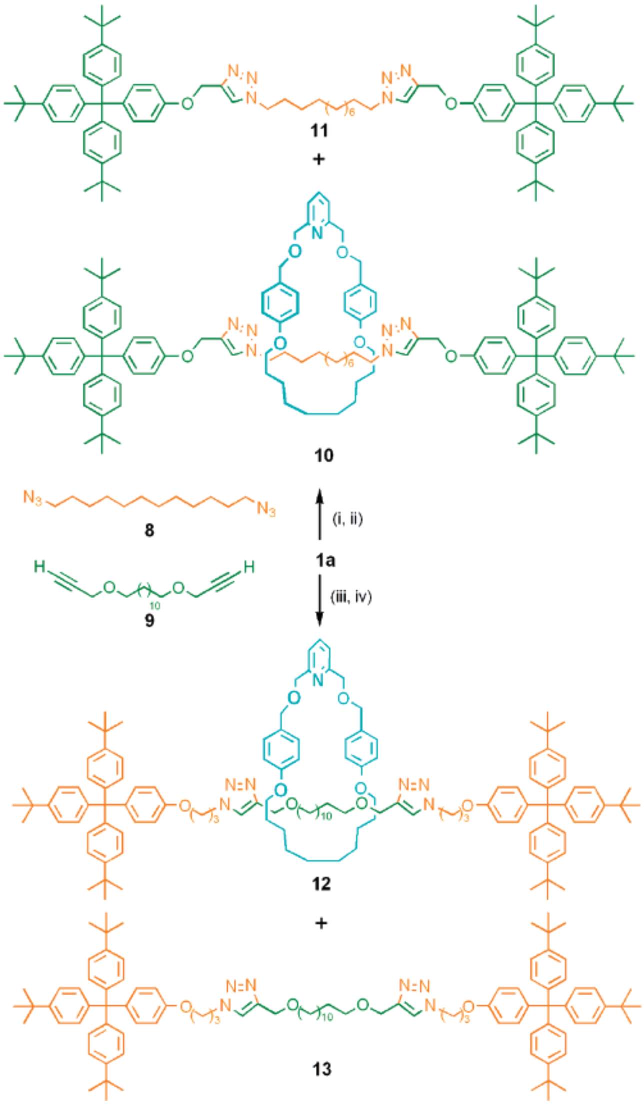
via simple π-coordinated complexes such as **II** (Scheme 3), the equivalent of intermediate A(ii) in Scheme 1.

The ^{1}H NMR spectra of [2]rotaxane **4l** and [3]rotaxane **7l** are shown in parts b and c, respectively, of Figure 6. The resonances for the axle (H_{f-j}) of the rotaxanes are shifted upfield compared to the signal for the free noninterlocked thread **5** (Figure 6a). The effect is more pronounced in the [3]rotaxane (Figure 6c) than in the [2]rotaxane (Figure 6b). Due to the asymmetry of the thread, the ^{1}H NMR spectrum of [3]rotaxane **7l** (Figure 6c) displays inequivalent but overlapping peaks for the two macrocycle components, which are double the intensity of the corresponding macrocycle signals in the [2]rotaxane. Single crystals of **7l** suitable for X-ray crystallography were grown by slow cooling of a hot saturated solution of **7l** in acetonitrile. The solid-state structure (Figure 7) confirmed the constitution of **7l** as a [3]rotaxane. Although it may superficially appear that face-to-face π-stacking interactions might aid the relative orientation of the two macrocycles on the thread, in the solid state the aromatic rings of adjacent macrocycles are not coplanar and their separation (>3.8 Å) is somewhat greater than that typically associated with aromatic stacking interactions.

Stoichiometric and Catalytic Active-Metal Template Synthesis of Bistriazole [2]Rotaxanes

To see whether the copper(I) would turn over catalytically during the formation of a single molecule, we investigated systems which require *two* cycloaddition reactions to be catalyzed in the formation of each molecule of [2]rotaxane (Scheme 4). [2]Rotaxanes **10** and **12** were each obtained in good yields (81% and 74%, respectively) using the conditions shown in Scheme 4 (0.5 equiv of Cu(I) for each triazole ring formed in a rotaxane) with either **1a**, **2**, and the diazide **8** or **1a**, **3**, and the dialkyne **9**. Since the rotaxane−Cu(I) complex in **4a** is strong enough to sequester the metal in the absence of pyridine, the lack of formation of more than trace amounts of [3]rotaxane in the reaction mixtures from Scheme 4 suggests that one macrocycle−Cu(I) complex may act processively to catalyze the formation of both triazole rings of an individual rotaxane thread. Such a hypothesis is consistent with the observation[25] by Rodionov et al. (albeit in a ligand-free Cu(I) system) of a strong kinetic enhancement in the second cycloaddition reaction when using diazide reactants. Reducing the amount of the copper salt to 20 mol % with respect to **1a** (10 mol % with respect to each

Scheme 4. Active-Metal Template CuAAC Synthesis of Bistriazole Molecular Shuttles **10** and **12**[a]



[a] Reagents and conditions: (i) **2**, [Cu(CH_3CN)$_4$](PF_6), CH_2Cl_2, 25 °C, 72 h; (ii) KCN, CH_2Cl_2/CH_3OH, 81% ([2]rotaxane **10**) over two steps with 0.5 equiv of Cu(I), 63% ([2]rotaxane **10**) over two steps with 0.1 equiv of Cu(I) + 3 equiv of pyridine; (iii) **3**, [Cu(CH_3CN)$_4$](PF_6), CH_2Cl_2, 25 °C, 72 h; (iv) KCN, CH_2Cl_2/CH_3OH, 74% ([2]rotaxane **12**) over two steps.

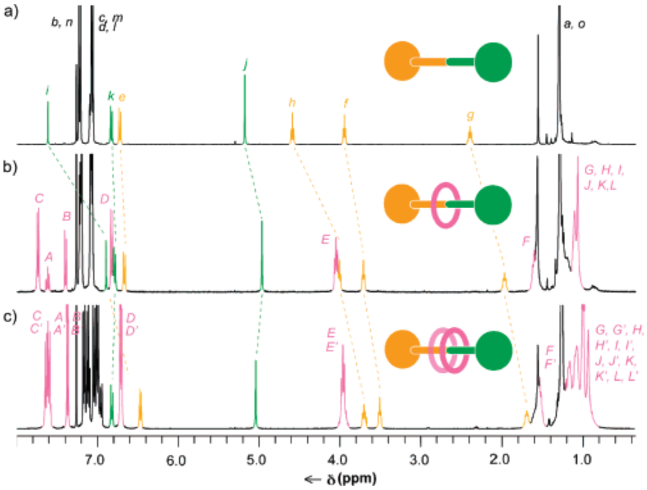


Figure 6. ^1H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) triazole thread **5**, (b) [2]rotaxane **4l**, and (c) [3]rotaxane **7l**. The assignments correspond to the lettering shown in Scheme 2 and Figure 4.

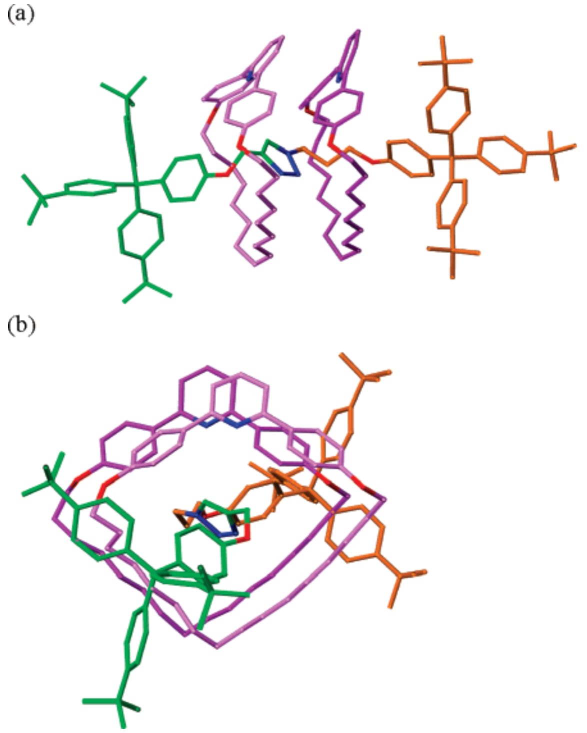


Figure 7. X-ray structure of [3]rotaxane **7l**, from a single crystal obtained from a saturated acetonitrile solution: (a) viewed side-on; (b) viewed along the axis of the thread. For clarity, different shades of purple are used for the carbon atoms of the two rings.

rotaxane triazole ring formed) and introducing 3 equiv of pyridine to the reaction of **1a**, **2**, and **8** to allow the processive catalyst to turn over intermolecularly still generated [2]rotaxane **10** in 63% yield (Scheme 4).

Transition-Metal-Mediated Control of the Shuttling Rate in Degenerate Two-Triazole-Station Molecular Shuttles

The shuttling of the ring in the degenerate two-station bistriazole rotaxane **10** in the presence of different diamagnetic transition-metal salts was investigated using ^1H NMR spectroscopy. Unlike most previously reported molecular shuttles—where the interactions used to direct the synthesis of the rotaxanes persist in the interlocked structure, resulting in a well-defined coconformation—there are no strong noncovalent interactions between the components of metal-free **10**. Comparison of the ^1H NMR spectrum of the free thread **11** (Figure 8a) with that of the rotaxane **10** (Figure 8b) shows uniform shielding of the thread signals (H_d, H_e, H_f, H_g, H_h), indicating that the macrocycle randomly explores the full length of the thread.

Reintroducing copper(I) into the bistriazole rotaxane[44] to form [Cu**10**](PF_6) (Scheme 5) gave a complex that exhibited fast shuttling of the macrocycle between the two triazole units in the room temperature ^1H NMR spectra in CD_3CN/CD_2Cl_2

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[44] For examples of 1,2,3-triazoles as ligands see refs 3, 6s, and 17a,b and (a) Liu, D.; Gao, W.; Dai, Q.; Zhang, X. *Org. Lett.* **2005**, *7*, 4907−4910. (b) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928−3934. (c) Mindt, T. L.; Struthers, H.; Brans, L.; Anguelov, T.; Schweinsberg, C.; Maes, V.; Tourwe, D.; Schibli, R. *J. Am. Chem. Soc.* **2006**, *128*, 15096−15097. (d) Suijkerbuijk, B. M. J. M.; Aerts, B. N. H.; Dijkstra, H. P.; Lutz, M.; Spek, A. L.; van Koten, G.; Klein Gebbink, R. J. M. *Dalton Trans.* **2007**, 1273−1276. (e) Huffman, J. C.; Flood, A. H.; Li, Y. *Chem. Commun.* **2007**, 2692−2694.

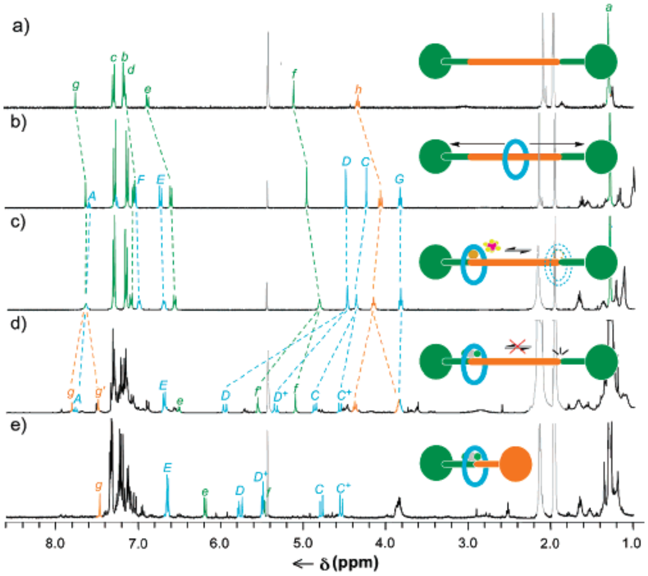


Figure 8. ^{1}H NMR spectra (400 MHz, CD_3CN/CD_2Cl_2 (9/1), 300 K) of (a) bistriazole thread **11**, (b) bistriazole [2]rotaxane **10**, (c) copper−bistriazole [2]rotaxane complex [Cu**10**](PF_6), (d) palladium dichloride−bistriazole [2]rotaxane complex Cl_2Pd**10**, and (e) palladium dichloride−triazole rotaxane complex Cl_2Pd**4a**. The assignments correspond to the lettering shown in Scheme 5.

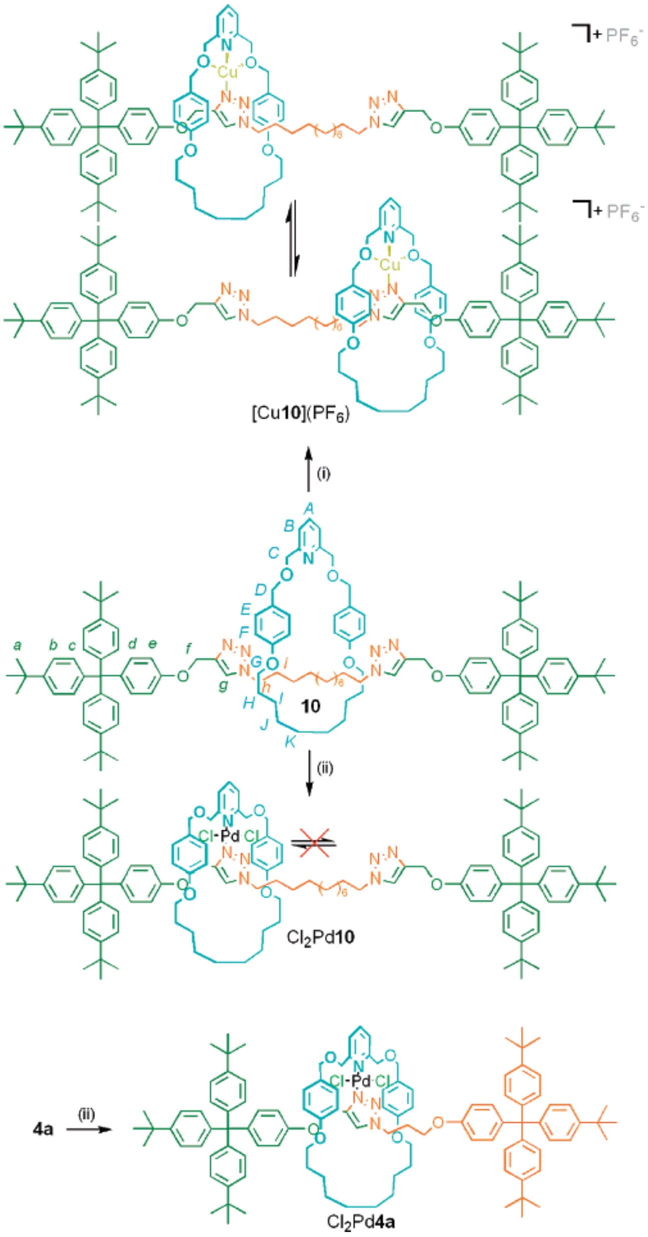
(Figure 8c).[45] Although fast shuttling between well-defined macrocycle binding sites is very unusual for metal-coordinated molecular shuttles,[46] Cu(I) complexes can exhibit extremely fast exchange rates.[47] In contrast to this dynamic behavior, the ^{1}H NMR spectrum (Figure 8d) of rotaxane **10** following coordination of $PdCl_2$ (Scheme 5, ii) displays two sets of peaks for protons close to the thread triazole rings (e.g., $H_{f/f'}$, $H_{g/g'}$). This observation is indicative of the macrocycle in the Cl_2Pd**10** complex being unable to shuttle between the triazole stations on the NMR time scale. This restriction to shuttling also manifests itself in the geminal splitting of the signals corresponding to H_C and H_D of the macrocycle, which occurs as a consequence of the two "faces" of the ring being in different chemical environments. The chemical shifts of one set of the duplicated signals (e.g., H_f) correspond closely to those of the free thread **11** (Figure 8a). The other set of duplicate signals (e.g., $H_{f'}$) correspond closely to a model single-triazole rotaxane−$PdCl_2$ complex, Cl_2Pd**4a** (Figure 8e, Scheme 5). Heating the sample of Cl_2Pd**10** to 343 K (close to the solvent boiling point of CD_3CN) did not lead to any broadening of the signals in the ^{1}H NMR spectrum, indicating that the macrocycle shuttling is very effectively blocked by coordination to Pd.

The notable features of these degenerate two-station bistriazole rotaxanes are the following:

(i) To our knowledge these are the first examples of molecular shuttles containing two degenerate transition-metal-binding stations.

(ii) The dynamics of the macrocycle exchange between the two well-defined discrete binding sites can be controlled with remarkable ease, simply through the judicious choice of different transition-metal ions.

Scheme 5. Controlling the Dynamics of Bistriazole Molecule Shuttle **10** by Coordination to Cu(I) or Pd(II)[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$ (1 equiv), CD_2Cl_2 (90%)/CD_3CN (10%), 25 °C, 5 min, >99%; (ii) $Pd(CH_3CN)_2Cl_2$ (1 equiv), CD_2Cl_2 (90%)/CD_3CN (10%), 25 °C, 5 min, >99%.

(iii) An active-metal template strategy is much more amendable to the synthesis of such shuttles than traditional (passive) metal template strategies, because the number of binding sites in the products is not necessarily related to the number of template sites used for the shuttle synthesis.

Conclusions

The Cu(I)-catalyzed 1,3-cycloaddition of azides with terminal alkynes is a highly effective reaction for the active-metal template synthesis of rotaxanes, as illustrated through both stoichiometric (up to 97% yields) and catalytic (up to 82% yields) versions of the strategy. The reaction tolerates a wide

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(45) We were unable to slow the macrocycle shuttling dynamics in [Cu(**10**)](PF_6) sufficiently, nor isolate that motion from other conformational processes at low temperatures, to determine an accurate shuttling rate.
(46) Durola, F.; Sauvage, J.-P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3537−3540.
(47) For an evaluation of ligand exchange rates at Cu(I) centers, see: Riesgo, E.; Hu, Y.-Z.; Bouvier, F.; Thummel, R. P. *Inorg. Chem.* **2001**, *40*, 2541−2546.

variety of both monodentate and bidentate macrocyclic ligands which, although inherently slower in promoting covalent bond formation than the ligand-free[23] Cu(I)-catalyzed reaction, all work by sequestering the majority of the Cu(I) present so that the rotaxane-forming CuAAC reaction becomes competitive with—and under many conditions dominates—the ligand-free CuAAC reaction. The addition of pyridine enables the Cu(I) active-metal template to turn over without significantly compromising the rotaxane yield. Among several potentially attractive features of this type of synthetic strategy is that it offers an unusual experimental probe of the reaction mechanism. The increase in rates of rotaxane formation by excess ligand-free Cu(I) supports the suggestion that in CH_2Cl_2 the copper σ-acetylide is activated by coordination to a second ligandless copper atom, and the sluggish reaction rates and remarkable formation of [3]rotaxanes with monodentate macrocycles at high macrocycle:Cu(I) ratios suggest that, under these conditions, the CuAAC reaction proceeds via a doubly bridged two copper atom intermediate (type B(ii), Scheme 1) when using a monodentate macrocyclic ligand and a simpler π-coordinated two copper atom intermediate (type A(ii), Scheme 1) when using a bidentate macrocyclic ligand.[48]

The experimental results concerning the active-metal template CuAAC synthesis of bistriazole rotaxanes suggest that the macrocycle−Cu(I) complex may act processively to catalyze the formation of more than one triazole ring per thread molecule. The resulting two-triazole-station molecular shuttles have interesting and unusual dynamic properties: coordination of the rotaxane macrocycle to Cu(I) gives a metal-complexed shuttle in which the ring still shuttles rapidly between the two triazole units of the thread, even at low temperatures in noncoordinating solvents. In contrast, complexation of the same two-triazole-station shuttle to $PdCl_2$ gives a rotaxane in which shuttling does not occur even at 343K in the presence of d_3-acetonitrile.

The template-directed assembly of otherwise difficult-to-access molecular architectures and the catalysis of covalent bond formation are two of the most useful tasks that transition metals can perform in organic chemistry. The active-template concept combines these two apparently disparate functions into one, which can produce—as the present work exemplifies—high-yielding, mild and effective synthetic routes to complex molecular structures requiring only catalytic quanitities of metal. The development of other active-template systems is in progress.

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

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(48) Note added in proof: Very recent calculations (Straub, B. F. *Chem. Commun.* published online 12th July 2007 DOI: 10.1039/b706926j) suggest that the metallacycle formed in Scheme 1 consists of a strain-free Cu-C(Cu)=C unit rather than the depicted Cu=C=C unit. The second copper atom in the type B(ii) and A(ii) reactive intermediates shown in Scheme 1 means they are perfectly set up to form such a Cu-C(Cu)=C metallacycle.