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Two Axles Threaded Using a Single Template Site: Active Metal Template Macrobicyclic [3]Rotaxanes

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Abstract: Template approaches to rotaxanes normally require at least $n - 1$ template sites to interlock n components. Here we describe the one-pot synthesis of [3]rotaxanes in which a single metal template site induces formation of axles through each cavity of a bicyclic macrocycle. Central to the approach is that a portion of the bicyclic molecule acts as a ligand for a transition metal ion that mediates covalent bond formation through one or other macrocyclic cavity, depending on the ligand's orientation, making a mechanical bond. The ligand can then rotate so that the transition metal can catalyze the formation of a second axle through the other macrocycle. Using this strategy with the Cu(I)-catalyzed azide−alkyne cycloaddition (the CuAAC reaction) generates a [3]rotaxane with two identical axles in up to 86% yield. [3]Rotaxanes with two different axles threaded through the macrobicyclic rings can also be created using a single template site, either by having copper(I) sequentially form both mechanical bonds (via the CuAAC reaction) using different sets of building blocks for each axle or by using two different reactions catalyzed by two different metal ions: a palladium(II)-mediated alkyne homocoupling to assemble the first thread through one cavity, followed by a copper(I)-mediated CuAAC reaction to form the second axle through the other ring.

Introduction

In recent years, template strategies have allowed increasingly elaborate structures featuring multiple mechanical bonds to be constructed.[1] Various examples of rotaxanes,[2] pseudo-rotaxanes,[3] catenanes,[4] and other types[5] of molecular links with three or more mechanical bonds or components have been described. Systems with multiple mechanical bonds between components that are also covalently connected have also been prepared.[6−8] However, the vast majority of [n]rotaxanes with $n > 2$ components consist of $n - 1$ rings encircling a single thread (linear[2a,c,h,j,m−o,q] or branched[2b,e,j−l,p]),

while rotaxanes consisting of multiple threads passing through rings are still rare.[2j,r,u,w] A feature common to almost[2n] all these synthetic strategies is that at least $n - 1$ template sites are normally required to interlock n components. Here we report on the synthesis of [3]rotaxanes in which a single metal template site sequentially induces formation of an axle through each cavity of a bicyclic ring system. The methodology relies on "active template"[9] rotaxane formation, in which a coordinated metal ion acts as both the template for the interlocked product and as a catalyst for promoting the formation of the crucial covalent bond that captures the threaded architecture. Active template synthesis has previously been used with a range of transition metal-catalyzed reactions to construct simple rotaxanes with macrocycles threaded onto a single axle. However, since the transition metal catalyst/template does not bind more strongly to the product than the starting material, it can in some cases[9a,c−e] turn over during the reaction. It seemed possible that by positioning the ligand at the junction between two macrocycle cavities the single template site might be able to direct active template reactions through each ring. Indeed, our investigation showed that two axles could be successfully threaded in this way, either by forming them using the same reaction (e.g., the Cu(I)-catalyzed azide−alkyne cycloaddition−the CuAAC reaction[10]) or via two different reactions which utilize different transition metal ions (the CuAAC reaction and a Pd(II)-catalyzed alkyne homocoupling[11]).

Results and Discussion

Macrobicyclic [3]Rotaxanes with Identical Axles. The synthesis of doubly threaded [3]rotaxanes is significantly compli-

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cated by the sheer size of the "stoppers" required to prevent dethreading of large rings.[2r,u,12] When contemplating how to achieve multiple threading with active template reactions that turn over, we were intrigued by the idea of incorporating the ligating site within a flexible bridging unit that bisected a large macrocycle into a bicyclic system. This should allow the ligand to orient the metal ion toward each cavity in turn, catalyzing covalent bond formation between appropriately derivatized building blocks through each cavity, producing [3]rotaxanes (Figure 1).

Bicyclic macrocycle **1a** (Scheme 1 and Figure 2) incorporates a 2,6-disubstituted pyridine unit (previously employed as the ligating motif in the active template synthesis of simple [2]rotaxanes[9a,c−e]) in a bridge separating two identical cavities. CPK models indicated that with C_{14} alkyl chains ($n = 2$, Scheme 1) the rings should be large enough to accommodate a thread unit through each cavity while a tris(*tert*-butyl)-substituted trityl group should be a sufficiently large stoppering group to prevent dethreading. The synthesis of **1a** was achieved in eight steps from the commercially available dimethyl acetal of 2,6-dihydroxylbenzoic acid (for details of the synthesis see the Supporting Information). Single crystals of a metal-coordinated
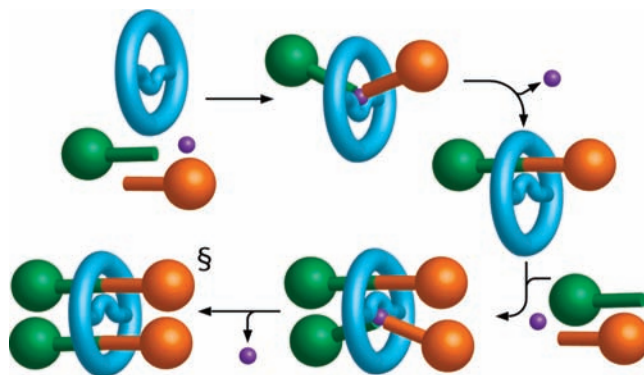

Figure 1. Active template synthesis of macrobicyclic [3]rotaxanes. The metal (purple) coordinates to the binding site. The metal can then promote formation of a covalent bond through each cavity of the macrocycle in turn, generating a doubly threaded [3]rotaxane. If the second thread forms significantly more slowly than the first (negative allostery), then the reaction can effectively be stopped at the intermediate [2]rotaxane stage and a different set of building blocks or even a different metal employed in a different active template reaction to form the second thread of the macrobicyclic [3]rotaxane. §If the threads being formed are not symmetrical through the mirror plane formed by the macrocycle, two different diastereoisomers (syn and anti arrangements of the threads) can be formed even though the threads themselves may be constitutionally identical.

1a complex suitable for X-ray analysis were obtained by slow cooling of a saturated solution of **1a**·PdCl$_2$(MeCN) in acetonitrile and the solid state structure (Figure 2) clearly shows the metal center orienting its chloride ligands so that they protrude through opposite sides of one of the macrocyclic cavities, as required by a rotaxane-forming active template mechanism.[9]

Carrying out the CuAAC reaction[9a,d] between alkyne **2** and azide **3** (5 mol equiv of each) with a stoichiometric quantity of CuPF$_6$ and bicyclic macrocycle **1a** in 1,2-dichloroethane at 70 °C over 24 h generated [2]rotaxane **5a**, which was isolated in 41% yield after demetalation with a basic ethylenediaminetetraacetic acid−ammonia (EDTA−NH$_3$) solution (Scheme 1; Table 1, entry 1). However, despite using a large excess of the alkyne and azide building blocks, only a small amount ($\leq 10\%$)

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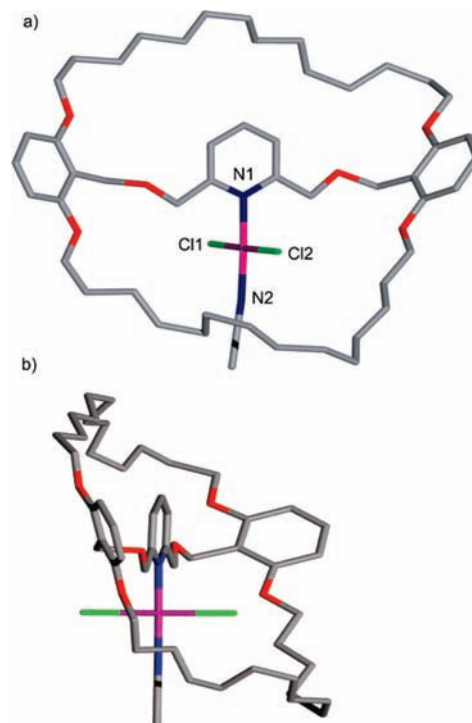
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Scheme 1. Synthesis of Macrobicyclic [2]- and [3]Rotaxanes via an Active Template CuAAC Reaction[a]
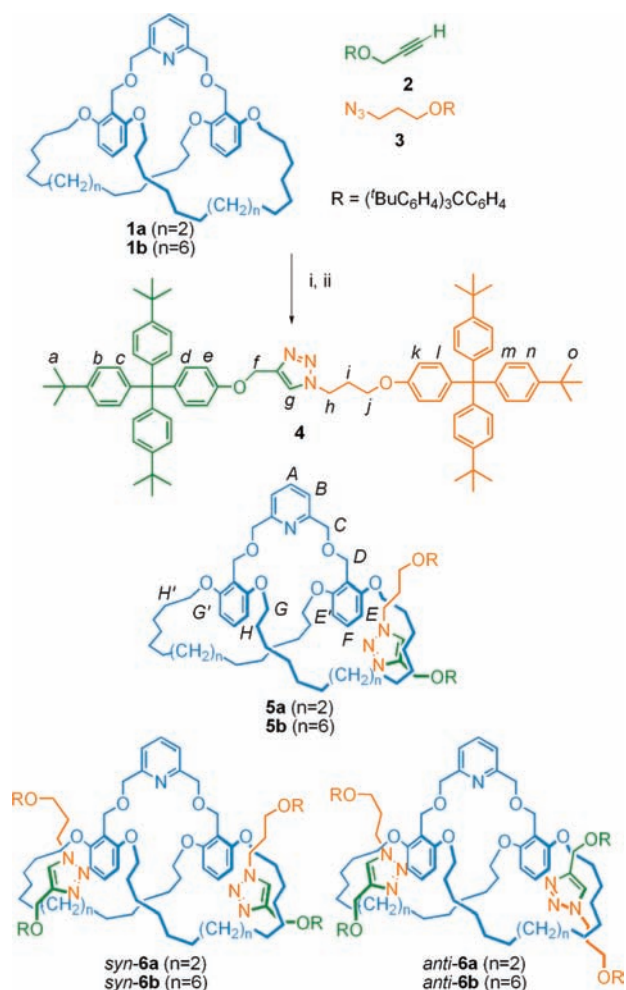
[a] Reagents and conditions: (i) [Cu(CH₃CN)₄]PF₆, ClCH₂CH₂Cl, 70 °C; (ii) EDTA, NH₃.

of the accompanying [3]rotaxane **6a** was formed (Table 1, entry 1). It seemed that the low yield of [3]rotaxane **6a** might be a result of the second cavity becoming too congested to accommodate a threading reaction following formation of [2]rotaxane **5a**. We therefore synthesized macrocycle **1b** (see Supporting Information), which possessed an additional four methylene units in each of the macrocyclic rings. Pleasingly, treating this larger bicyclic structure (**1b**) with CuPF₆ and 5 mol equiv (2.5 equiv per macrocycle) of **2** and **3** furnished [2]rotaxane **5b** in 57% yield together with 40% of [3]rotaxane **6b**, a combined 97% yield of interlocked products (Table 1, entry 2). Following further addition of azide and alkyne (5 equiv of each), the yield of [3]rotaxane **6b** was increased to 86% (Table 1, entry 3).

The structures of the [2]- and [3]rotaxanes were established unambiguously by mass spectrometry and NMR spectroscopy

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Figure 2. X-ray crystal structure of **1a**·PdCl₂(MeCN), from a single crystal obtained by slow cooling of a saturated acetonitrile solution. Nitrogen atoms are shown in blue, oxygen atoms are red, chlorine atoms are green, and palladium is pink. Selected bond lengths (Å) and angles (deg): N1–Pd, 2.02; N2–Pd, 2.01; Cl1–Pd, 2.28; Cl2–Pd, 2.29; Cl1–Pd–Cl2, 178.0. Structure viewed (a) in the plane of the pyridine ring and (b) to show the Cl1–Pd–Cl2 axis directed through one of the macrocyclic rings.

Table 1. Conversion of **1a** and **1b** to Macrobicyclic [2]-and [3]Rotaxanes (Scheme 1)

| entry	macrocycle	equiv 2 and 3	[2]rotaxane yield[a]	[3]rotaxane yield[a]
1[b]	**1a**	5.0	41% (**5a**)	≤10% (**6a**)[c]
2[b]	**1b**	5.0	57% (**5b**)	40% (**6b**)
3[d]	**1b**	10.0[e]	14% (**5b**)	86% (**6b**)

[a] Yields based on macrocycle **1**. [b] Reaction carried out over 24 h. [c] Yield determined by ¹H NMR. [d] Reaction carried out over 48 h. [e] Five equivalents of each of **2** and **3** was introduced at the start of the reaction and again after 24 h.

(see Supporting Information). Comparison of the ¹H NMR spectrum of [2]rotaxane **5b** (Figure 3b) with those of its noninterlocked components (macrocycle **1b** and thread **4**; Figure 3 panels a and d, respectively) shows upfield shifts of protons of the axle (H_f, H_h, and H_k) and macrocycle (H_A, H_E, and H_G) arising from these regions of the mechanically threaded components spending significant amounts of time face-on to aromatic rings. As only one of the two macrocycle cavities is threaded by an axle in [2]rotaxane **5b**, the bicyclic host is desymmetrized with respect to the parent compound **1b** (Figure 3a) and the ¹H NMR spectrum of the [2]rotaxane is correspondingly more complex (note, for example, H_C, H_D, and H_E in

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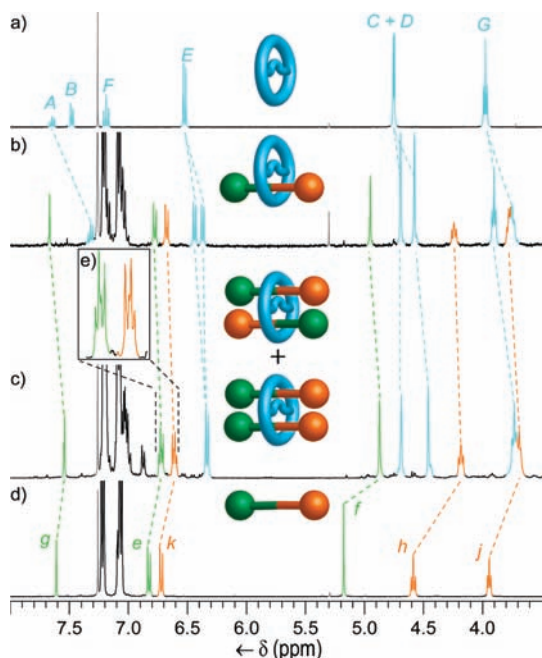
Figure 3. Partial ^{1}H NMR spectra (400 MHz, CDCl$_3$, 298 K) of (a) macrocycle **1b**, (b) [2]rotaxane **5b**, (c) [3]rotaxane *syn/anti*-**6b**, (d) noninterlocked thread **4**, and (e) expansion of the region showing resonances H$_e$ and H$_k$ in [3]rotaxane *syn/anti*-**6b**. The lettering corresponds to that shown in Scheme 1.

Figure 3b cf. Figure 3a). Penetration of axles through both macrocycle cavities in [3]rotaxane **6b** simplifies the ^{1}H NMR spectrum compared to that of [2]rotaxane **5b**, and the H$_E$ and H$_G$ protons associated with each cavity produce coincident resonances (Figure 3c). This is in spite of the potential for stereoisomerism present in [3]rotaxane **6b**, which can exist as both syn or anti diastereomers depending on whether the axles are threaded in the same direction (syn isomer) through the cavities or in opposite directions (anti isomer), both of which would be expected to be produced in the [3]rotaxane-forming reaction (Scheme 1). Although we could not find HPLC conditions under which the isomers of **6b** were resolved, close examination (Figure 3e) of the signals corresponding to H$_e$ and H$_k$ reveals that they both appear as doubled sets of signals in [3]rotaxane **6b**, suggesting that both stereoisomers are indeed present in the [3]rotaxane reaction product but that they are almost indistinguishable by ^{1}H NMR.

Macrobicyclic [3]Rotaxanes with Different Axles Assembled by Successive Active Template CuAAC Reactions. We next investigated whether the single template site could be used sequentially for the synthesis of [3]rotaxanes in which the thread components are nonidentical. The slower formation of the axle through the second cavity (a form of negative allosteric regulation[13]) of **5b** allows the [2]rotaxane to be isolated in good

Scheme 2. Synthesis of a [3]Rotaxane with Two Different Triazole Threads via Successive CuAAC Active Template Reactions^a
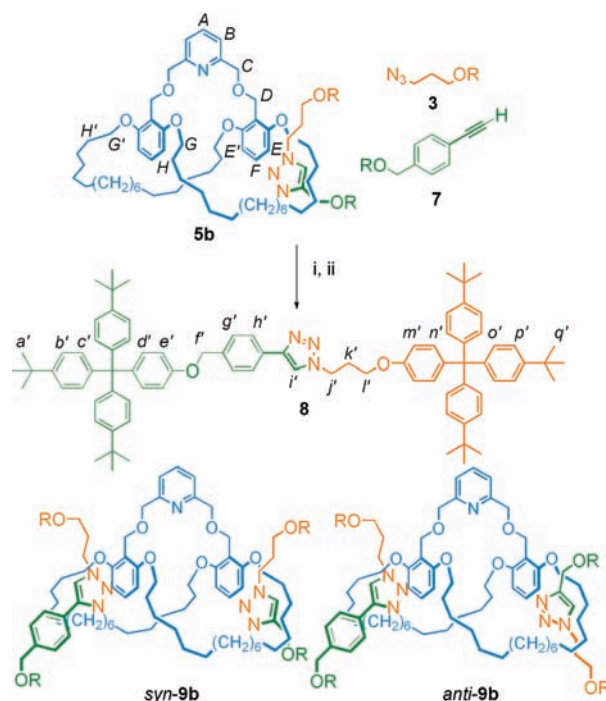

^{a} Reagents and conditions: (i) [Cu(CH$_3$CN)$_4$]PF$_6$, ClCH$_2$CH$_2$Cl, 70 °C; (ii) EDTA, NH$_3$. 43%.

yield (Table 1, entry 2). Carrying out a second active template CuAAC reaction on this [2]rotaxane intermediate utilizing alkyne **7** in place of alkyne **3** (Scheme 2) generated [3]rotaxane *syn/anti*-**9b,** with different triazole axles threaded through the two macrocycles, in 43% yield (Scheme 2). In the ^{1}H NMR spectrum of *syn/anti*-**9b** (Figure 4b) the formation of the second mechanical bond with a different (unsymmetrical) thread does not give a simplified spectrum of the bicyclic macrocycle component in the manner observed for **6b** (Figure 3c), with the signals corresponding to H$_E$, for example, clearly arising from two chemically different sets of protons.

Macrobicyclic [3]Rotaxanes with Different Axles Assembled Using Two Different Chemical Reactions. Finally, we attempted the synthesis of [3]rotaxanes using two different active template reactions (catalyzed by different transition metals) to sequentially assemble the two threads via the single template site. A Pd(II)-catalyzed alkyne homocoupling[11] was selected as the second axle-forming reaction as it has previously been successfully used[9e] to assemble simple [2]rotaxanes via active template syntheses using a 2,6-disubstituted pyridine unit as the ligating group. However, when [2]rotaxane **5b** was subjected to these reaction conditions with alkyne **10**, no [3]rotaxane was detected in the reaction mixture. We reasoned that this could be because

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(8) For examples of [2]rotaxanes derived from bicyclic macrocycles, see: (a) Mahoney, J. M.; Shukla, R.; Marshall, R. A.; Beatty, A. M.; Zajicek, J.; Smith, B. D. *J. Org. Chem.* **2002**, *67*, 1436–1440. (b) Li, S. J.; Liu, M.; Zhang, J. Q.; Zheng, B.; Zhang, C. J.; Wen, X. H.; Li, N.; Huang, F. H. *Org. Biomol. Chem.* **2008**, *6*, 2103–2107. (c) Wang, F.; Zhou, Q. Z.; Zhu, K. L.; Li, S. J.; Wang, C.; Liu, M.; Li, N.; Fronczek, F. R.; Huang, F. *Tetrahedron* **2009**, *65*, 1488–1494. (d) Klivansky, L. M.; Koshkakaryan, G.; Cap, D.; Liu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4185–4189. (e) Li, S. J.; Liu, M.; Zheng, B.; Zhu, K. L.; Wang, F.; Li, N.; Zhao, X. L.; Huang, F. H. *Org. Lett.* **2009**, *11*, 3350–3353.
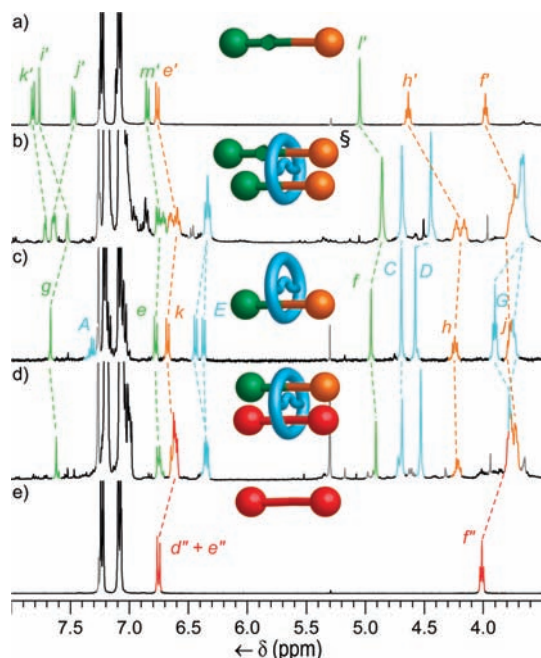
Figure 4. Partial ^{1}H NMR spectra (400 MHz, CDCl₃, 298 K) of (a) noninterlocked thread **8**, (b) mixed-triazole-thread [3]rotaxane *syn/anti*-**9b**, (c) [2]rotaxane **5b**, (d) bisacetylene-thread-triazole-thread [3]rotaxane **10b** and (e) noninterlocked thread **11**. The lettering corresponds to that shown in Schemes 2 and 3. The [3]rotaxane spectra contain minor impurities that we were unable to fully remove. §Mixture of syn and anti isomers.

the triazole ring of the already threaded axle in **5b** could potentially coordinate[14] to the Pd(II) and inhibit the second active template reaction. We therefore tried switching the order in which the axles were formed, attempting to form the threaded axle from the active template Pd(II)-alkyne homocoupling first and then applying the Cu(I)-catalyzed alkyne–azide cycloaddition with fresh alkyne and azide building blocks (Scheme 3).

The reaction sequence was carried out without purification of the intermediate [2]rotaxane (**12b**). Bicyclic macrocycle **1b** was subjected to the Pd(II)-mediated alkyne homocoupling conditions (5 mol % **1b**·PdCl₂(MeCN), 30 equiv **10**, *i*Pr₂NH, CuI, I₂, benzene) with stoppered alkyne **10**. After 5 days, all the alkyne had been consumed although ^{1}H NMR suggested only ~10% conversion to the [2]rotaxane, **12b**, which was not isolated. The solution was extracted with Na₄EDTA and filtered to remove residual Pd, and then the reaction vessel was charged with azide and alkyne building blocks **3** and **4** and the Cu(I)PF₆

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Scheme 3. Synthesis of a [3]Rotaxane with Bisacetylene and Triazole Threads via Sequential Active Template Reactions[a]
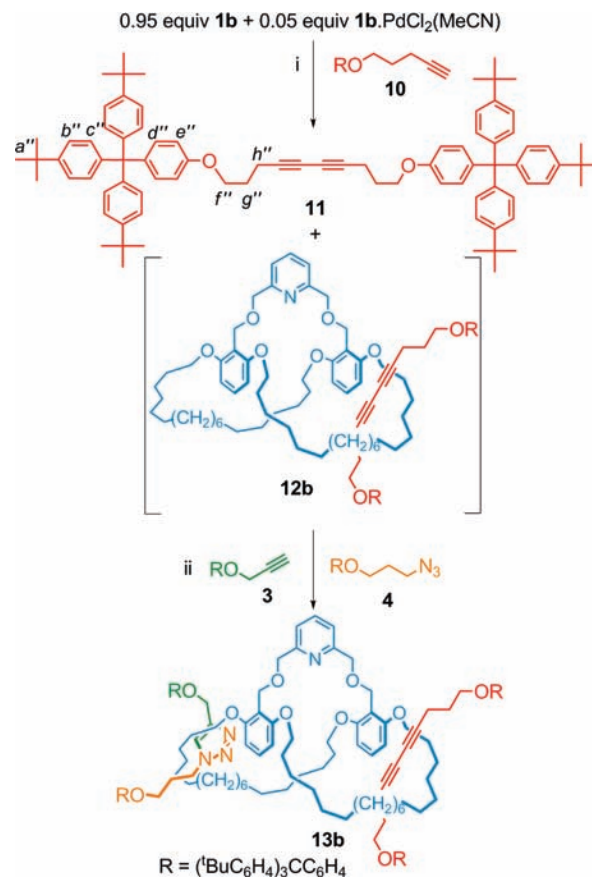
[a] Reagents and conditions: (i) **10** (30 equiv), diisopropylamine (10 equiv), CuI (2 equiv), I₂ (0.5 equiv), room temp, benzene; (ii) (1) alkyne **3** (5 equiv), azide **4** (5 equiv), [Cu(CH₃CN)₄]PF₆, ClCH₂CH₂Cl, 70 °C; (2) EDTA, NH₃; 4% yield over both mechanical bond-forming steps: ~10% for the first (formation of **12b**); ~40% for the second (formation of **13b**). For full details of experimental procedures see the Supporting Information.

catalyst and subjected to the CuAAC reaction conditions. [3]Rotaxane **13b**, with both bisacetylene and triazole threads was isolated in 4% yield over these two synthetic steps (Scheme 3). While the yield is certainly modest (largely the result of the Pd(II)-promoted homocoupling being so poor, the second axle is threaded through the [2]rotaxane intermediate **12b** in ~40% yield), it nonetheless demonstrates that it is possible to direct

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two different metal-catalyzed reactions sequentially through different (chemically identical) cavities through the action of one bridging ligating group. As with the other rotaxanes reported in this paper, [3]rotaxane **13b** was unambiguously characterized by NMR spectroscopy and mass spectrometry (see Supporting Information). The ¹H NMR of [3]rotaxane **13b** (Figure 4d) is not complicated by the diasteroisomerism present in *syn/anti-***6b** and *syn/anti-***9b** since the bisacetylene thread component is symmetrical.

Conclusions

We have demonstrated that it is possible for a suitably located ligand to successively promote covalent bond forming reactions through each cavity of a bicyclic structure, a coordinated transition metal ion simultaneously acting as a catalyst and a template for mechanical bond formation each time. Using the CuAAC reaction of azide and alkyne building blocks, the formation of [3]rotaxanes is remarkably effective, proceeding in up to 86% yield (>94% per axle). Even with this first generation system it is possible to form two mechanical bonds

with different axles, although this is less efficient (65% per axle using the CuAAC reaction twice), particularly when employing chemical reactions catalyzed by different metal ions (~10% and ~40%, respectively, for a Pd(II)-catalyzed alkyne homocoupling followed by a Cu(I)-catalyzed CuAAC reaction). The ability to form multiple mechanical bonds via a single template site is a potentially significant addition to the toolbox for interlocked molecule assembly. It may prove useful for constructing heterocircuit Borromean rings,[15] for example, (through the use of cleavable bridging ligands) and other currently inaccessible higher order links that require the threading of multiple different axles through large rings.

Supporting Information Available: Experimental procedures and spectral data for all compounds and the details of the X-ray analysis of **1a**·PdCl₂(MeCN) including cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

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