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A One-Pot Synthesis of Constitutionally Unsymmetrical Rotaxanes Using Sequential Cu^{I}-Catalyzed Azide–Alkyne Cycloadditions

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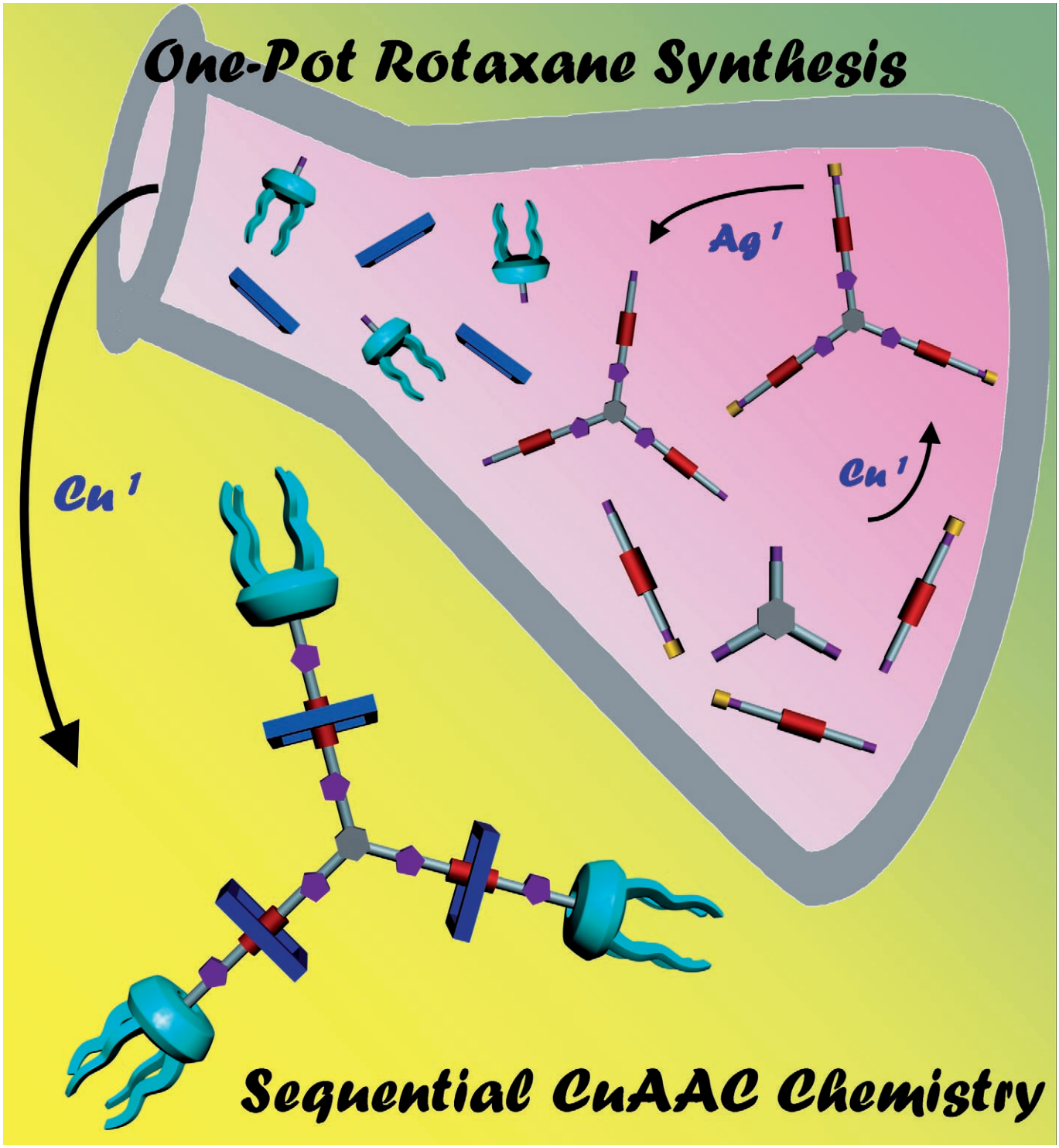

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Abstract: A one-pot sequential Cu^{I}-catalyzed azide–alkyne cycloaddition (CuAAC) strategy is presented for the synthesis of constitutionally unsymmetrical cyclobis(paraquat-*p*-phenylene)-based rotaxanes in good yields from simple starting materials. The methodology consists of performing multiple CuAAC reactions to stopper a pseudorotaxane in a stepwise manner, the order of which is controlled through silyl-protection and Ag^{I}-catalyzed deprotection of a terminal alkyne. The methodology is highlighted by the synthesis of an amphiphilic branched [4]rotaxane. The methodology increases the ability to access ever more complicated mechanically interlocked compounds to serve in devices as sophisticated and functional molecular machinery.

Keywords: cycloaddition · mechanical bonds · rotaxanes · supramolecular chemistry · template-directed synthesis

Introduction

Highly efficient and convergent strategies for the synthesis of mechanically interlocked compounds are essential in order to facilitate the development of sophisticated and functional artificial molecular machinery.[1] In this context, we recently developed[2] a simple and high-yielding method for the synthesis of donor–acceptor rotaxanes[3,4] based on a threading-followed-by-stoppering approach[5] that utilizes the Cu^{I}-catalyzed azide–alkyne cycloaddition (CuAAC).[6] Although we have employed[2–4] this method to prepare previously unavailable mechanically interlocked compounds, it is best suited for the template-directed synthesis[7] of [*n*]rotaxanes stoppered by identical bulky groups. Rotaxanes that incorporate two different stoppers, such as the amphiphilic bistable [2]rotaxanes[8] used as the storage elements in crossbar memory circuits,[1f,9] represent a significant increase in structural complexity and are thus even more challenging synthetic targets. Herein, we report 1) the extension of a general, one-pot method[10] that uses sequential CuAAC reactions to address this challenge, and 2) demonstrate its application to the highly convergent synthesis of an amphiphilic [4]rotaxane.

A sequence of two or more CuAAC reactions may be controlled (Figure 1) through **I**) performing the reaction of the desired azide and alkyne partners in the presence of another masked reactive functionality, **II**) removing the masking group to present another reaction partner, and **III**) repeating the CuAAC reaction of the unmasked functionality. These sequences would prove most efficient if they could be performed in one-pot, a goal that adds the requirements that each of the three (or more) steps must proceed to nearly quantitative conversion and that the reagents used in the beginning of the sequence must not interfere with those employed in subsequent steps. Such a sequence was devised[10] for the covalent attachment of peptide building blocks to a central unit directed by a silyl protecting group. The extension of such a method to mechanical bond formation adds several challenges, most prominently, the need for all components of sensitive donor–acceptor mechanically interlocked compounds to tolerate each of the steps of a sequential CuAAC method. The ring most commonly employed in donor–acceptor mechanically interlocked com-

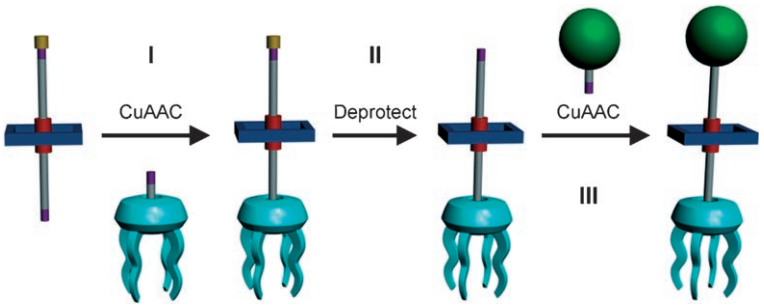

Figure 1. Graphical representation of the sequential CuAAC strategy applied to the synthesis of mechanically interlocked molecular compounds. A constitutionally unsymmetrical monoprotected pseudorotaxane may be stoppered in the initial step (**I**), the protecting group removed in the second step (**II**), and then functionalized with a different type of stopper in the third step (**III**) to form a constitutionally unsymmetrical [2]rotaxane. The use of a multifunctional stopper allows higher order rotaxanes (e.g., the branched [4]rotaxane described in this article) to be assembled sequentially in one pot.

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Supporting information for this article (2D and VT ^{1}H NMR spectra of the [4]rotaxane **11**·12 PF_6 and the dumbbell compound **12**) is available on the WWW under http://www.chemeurj.org/ or from the author.

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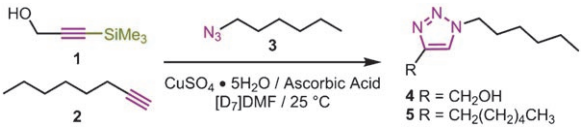
pounds, namely cyclobis(paraquat-*p*-phenylene) (**CBPQT**$^{4+}$), is sensitive to most bases, nucleophiles, and reducing agents, severely limiting the range and scope of reagents and conditions available to carry out the deprotection(s). The prevalent use of silyl groups for the protection of alkynes, and the availability of relatively mild methods for the deprotection of trimethylsilyl(TMS)-protected alkynes[11] in particular, led us to investigate this protecting group with the intention of developing a one-pot sequential CuAAC method compatible with the **CBPQT**$^{4+}$ ring and its donor–acceptor complexes.

Results and Discussion

As a preliminary appraisal of the ability of the TMS group to prevent a contiguous alkyne functionality from participating in the desired CuAAC reaction, 3-trimethylsilyl-2-propyn-1-ol (**1**) and 1-azidohexane (**3**) were treated (Table 1, entry 1) with the $CuSO_4$·$5H_2O$/ascorbic acid catalyst system in DMF.[12] Somewhat surprisingly, under these reaction conditions, significant amounts of the 1,2,3-triazole product **4** (54% conversion) were formed over the course of 24 h, presumably as a result of the slow hydrolysis of the TMS group. The protecting group did, however, slow down the CuAAC reaction substantially, and a competition experiment (Table 1, entry 2) between **1** and 1-octyne (**2**) in a CuAAC reaction with **3** resulted in excellent chemoselectivity for the formation of 1,4-dihexyl-1,2,3-triazole (**5**), despite the observation of partial hydrolysis of **1** to propargyl alcohol (8%) at the conclusion of the experiment. This test-bed work demonstrates that the TMS protecting group is sufficiently kinetically stable under the conditions of the CuAAC reaction, so much so that the cycloaddition occurs almost exclusively with the unprotected alkyne.

Table 1. Chemoselectivity between **1** and **2** in CuAAC reaction with **3** to form either **4** or **5**.

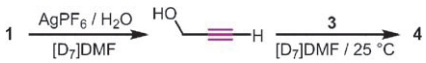


Entry	**1** : **2** : **3**	Time [h]	**4** : **5**	Conversion[a] [%]
1	1 : 0 : 1	24	1 : 0	54
2	1 : 1 : 1	16	1 : 99	96

[a] With respect to **3**, monitored by integration of ^{1}H NMR spectra.

Next, appropriate conditions for the sequential desilylation and CuAAC reactions required for the desired one-pot procedure (Table 2) were investigated. The Ag^I-catalyzed hydrolysis of TMS protected alkynes[11] was assumed to be sufficiently mild to ensure the survival of the **CBPQT**$^{4+}$. Indeed, 10 mol% $AgPF_6$ in the presence of H_2O (1 equiv per alkyne) catalyzed the hydrolysis of the TMS group, resulting (Table 2, entry 3) in nearly quantitative conversion in 18 h when the reaction mixture was heated to 40 °C. $AgPF_6$ was introduced into the reaction mixture in order to prevent counterion exchange and subsequent precipitation of Ag^I or **CBPQT**$^{4+}$-containing salts. Interestingly, the desilylation proceeded noticeably more slowly when the reaction was performed (Table 2, entry 5) in the presence of **CBPQT**$^{4+}$. No decomposition of the **CBPQT**$^{4+}$, however, was observed. Next, we developed conditions to effect the second CuAAC reaction in the presence of silver salts remaining from the deprotection. The $CuSO_4$·$5H_2O$/ascorbic acid catalytic system (5/10 mol%, respectively) formed (Table 2, entry 1) the CuAAC product, albeit somewhat slowly. Upon addition of the $CuSO_4$·$5H_2O$ and ascorbic acid, a silver mirror formed on the walls of the reaction vessel, most likely as a result of the reduction of Ag^I to Ag^0 by Cu^I and/or ascorbic acid, both processes that would impact negatively upon the availability of Cu^I required to catalyze the cycloaddition. Although the CuAAC reaction proceeds to higher conversions when an excess of ascorbic acid (1.3 equiv per alkyne; 6.3 equiv per **CBPQT**$^{4+}$) is used, the intensities of the broadened **CBPQT**$^{4+}$ resonances in the ^{1}H NMR spectrum of the reaction mixture were attenuated to 17% of their initial values. The excess of ascorbic acid ($E°=0.3$ V)[13] presumably reduces the **CBPQT**$^{4+}$ ($E°=-0.29$ and -0.71 V),[14] and while the reversibility of this process was not determined, reduced **CBPQT**$^{4+}$ derivatives do not bind electron rich guests. As an alternative to adding ascorbic acid at all, Cu^0 was used (Table 2, entry 2) as a copper source, which presumably *generates* the catalytically active Cu^I following oxidation by Ag^I. Indeed, this procedure did ultimately produce the desired CuAAC reaction, although we subsequently found that a small amount of additional $[Cu(MeCN)_4]PF_6$ helped to speed up the reaction (Table 2, entry 4) further, despite the fact that the addition of $[Cu(MeCN)_4]PF_6$ alone catalyzed the CuAAC reaction only slowly (Table 2, entry 3). Finally, it was confirmed that, when the above sequence is carried out in the presence of **CBPQT**$^{4+}$, the sequential deprotection/CuAAC reactions proceed (Table 2,

Table 2. Reaction condition development: one-pot TMS deprotection of **1** followed by CuAAC reaction of the generated alkyne.



Entry	Deprotection conditions (additive)	Conv. [%][a]	CuAAC reagents[b] (additive)	CuAAC time [h]	Conv. [%][c]
1	25 °C, 48 h	98[d]	$CuSO_4$·$5H_2O$ ascorbic Acid	90	45
2	25 °C, 48 h	98[d]	Cu nanopowder	90	>98
3	40 °C, 18 h	>98[e]	$[Cu(MeCN)_4]PF_6$	26	93
4	40 °C, 18 h	>98[e]	Cu nanopowder $[Cu(MeCN)_4]PF_6$	1	>98
5	40 °C, 54 h, (**CBPQT**·4PF_6)	90[e]	Cu nanopowder $[Cu(MeCN)_4]PF_6$ (**CBPQT**·4PF_6)	5	>98

[a] With respect to **1**, monitored by integration of ^{1}H NMR spectra. [b] **3** (1.1 equiv) was used. [c] With respect to propargyl alcohol intermediate. [d] 0.05 equiv of $AgPF_6$ was used. [e] 0.10 equiv of $AgPF_6$ was used.

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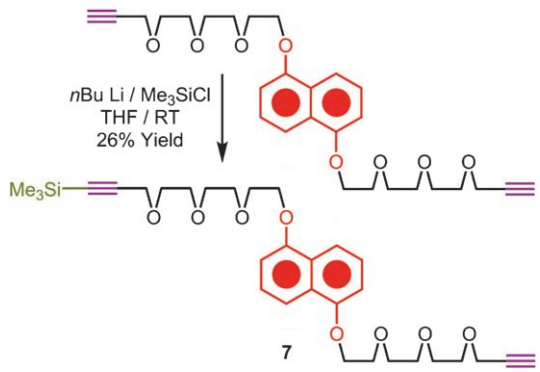
entry 5) to high conversion with no decrease in the intensities of the **CBPQT**$^{4+}$ ^{1}H NMR resonances.

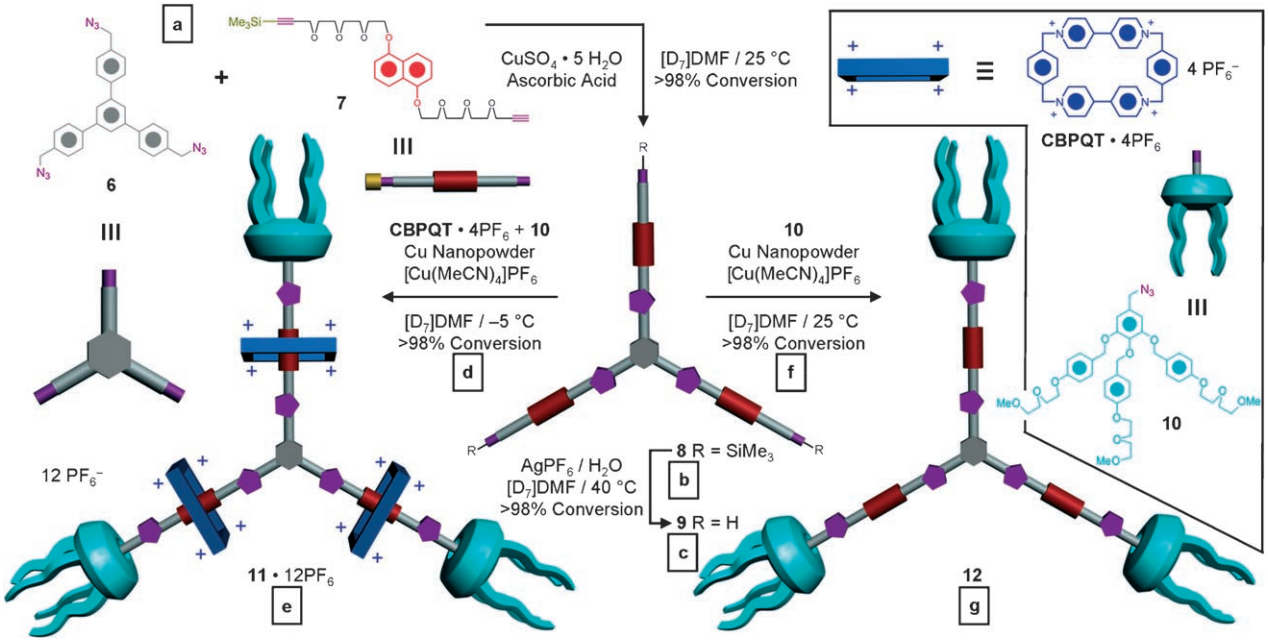
With the three-step sequential CuAAC methodology operating well in our hands, we envisioned that the sequential CuAAC reactions could be used to attach different stoppers to each end of a pseudorotaxane. Furthermore, in order to test this method for the synthesis of compounds with particularly complicated structures, a branched [4]rotaxane was chosen so that each CuAAC reaction and deprotection step would have to occur, not just once, but three times within each molecule. The threefold symmetry, previously incorporated into acid/base-switched molecular elevators[15,16] and present in the non-trivial amphiphilic [4]rotaxane **11**·12 PF_6 was accessed (Scheme 1) in one-pot by sequentially stoppering the constitutionally unsymmetrical dioxynaphthalene (DNP) derivative **7**, first with the trifunctional azide **6** and then subsequently with the monofunctional azide **10**. The DNP derivative **7** was synthesized (Scheme 2) bearing one TMS-protected alkyne and one terminal alkyne such that the constitutional asymmetry endowed by the TMS group would be expressed in the amphiphilic character of the final branched [4]rotaxane. The triazide **6** and monoazide **10** were each obtained (Scheme 3) through azide displacement of their benzyl chloride precursors.

Before attempting the template-directed synthesis of the [4]rotaxane, we first of all pursued (Scheme 1) the same reaction sequences—which we had in mind to prepare **11**·12 PF_6—to form the dumbbell compound **12**. The relative simplicity of the ^{1}H NMR spectrum of **12** compared to that (vide infra) of the [4]rotaxane was the motivation for us making the dumbbell compound first. By stoppering the monofunctional DNP derivative **7** in a controlled, sequential



Scheme 2. The synthesis of the constitutionally unsymmetrical DNP derivative **7**.

manner in the absence of **CBPQT**·4 PF_6, first with the triazide **6** and then subsequently with the monoazide **10**—following silyl deprotection of the protected alkyne—we anticipated obtaining compound **12** in high yield. This three-step reaction sequence was carried out in an NMR tube in [D_7]DMF such that each step of the reaction could be monitored (Figure 2) closely by ^{1}H NMR spectroscopy. Upon mixing the triazide **6** with the monoalkyne **7** in a 1:3 molar ratio, the first CuAAC reaction proceeded to form the tris-TMS-protected compound **8**, the outcome of which was confirmed by the transformation of the terminal alkyne proton resonance ($\delta = 3.39$ ppm in Figure 2a) of the DNP derivative **7** to the triazole proton resonance ($\delta = 8.25$ ppm in Figure 2b) of the tris-DNP intermediate **8**. The chemical shifts of the methylene group resonances neighboring the terminal alkyne and azide ($\delta = 4.22$ and 4.61 ppm, respectively, in Fig-



Scheme 1. Sequential CuAAC synthesis[a] of the [4]rotaxane **11**·12 PF_6 and the dumbbell compound **12**. [a] Labels for ^{1}H NMR spectroscopic monitoring of the reactions identified by boxed letters.

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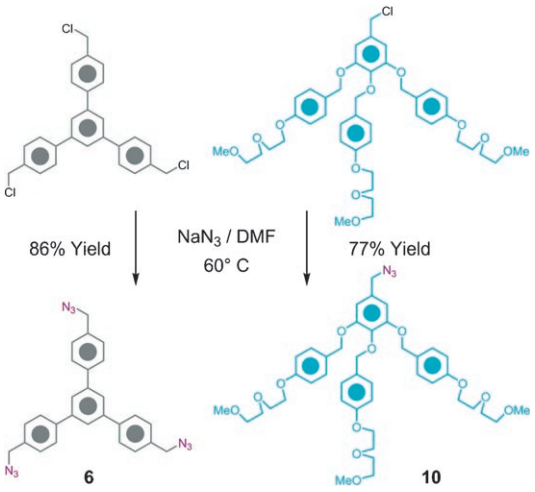

Scheme 3. The synthesis of the triazide **6** and the monoazide **10**.

ure 2a) are transformed into the methylene group resonances ($\delta = 4.62$ and 5.76 ppm in Figure 2b) neighboring the newly formed triazole. In keeping with the model experiments, some partial hydrolysis (17%) of the TMS protecting groups also occurred during the first CuAAC reaction of **6** with **7**. Even so, as indicated by the model experiments, the TMS group protects the alkynes to the extent that the CuAAC reaction occurs, forming **8** with a high conversion (>98% with respect to **6**). The Ag^{I}-catalyzed desilylation was then performed, affording the tris-alkyne **9**, once again in high conversion (>98%). Completion of the desilylation was confirmed by the migration and transformation of the methylene group singlet resonance ($\delta = 4.23$ ppm in Figure 2b) neighboring the silyl protected alkyne of **8** to a doublet ($\delta = 4.20$ ppm with $J^4 \approx 3$ Hz in Figure 2c) for the methylene group neighboring the terminal alkyne in **9**. This diagnostic splitting pattern is a result of long-range coupling between the liberated terminal alkyne proton and the neighboring methylene protons in **9**. Upon addition of 3.3 equivalents of the azide-containing hydrophilic precursor **10** (Figure 2f), the methylene peak ($\delta = 4.45$ ppm) neighboring the added azide was evident along with the terminal alkyne proton peak ($\delta = 3.38$ ppm) for the tris-alkyne **9**. Both of these peaks reappeared as another set of signals—for the methylene group next to a triazole ($\delta = 5.62$ ppm) and for the second triazole proton ($\delta = 8.33$ ppm) in Figure 2g—after the second (Cu-nanopowder/$[Cu(MeCN)_4]PF_6$-promoted) CuAAC reaction was carried out to form the final dumbbell compound **12** with >98% conversion with respect to tris-alkyne intermediate **9**.

With an intimate knowledge of the spectroscopic characteristics accompanying the sequential CuAAC reaction in the formation of the dumbbell compound **12**, the synthesis of the [4]rotaxane **11**·12PF_6 was attempted in a similar manner with periodic monitoring (Figure 3) by ^{1}H NMR spectroscopy. The steps leading to the formation of the tris-alkyne intermediate **9** were exactly the same as those followed in the synthesis of **12**. The addition of 3.3 equivalents of **CBPQT**·4PF_6 at −5°C to the intermediate **9** resulted

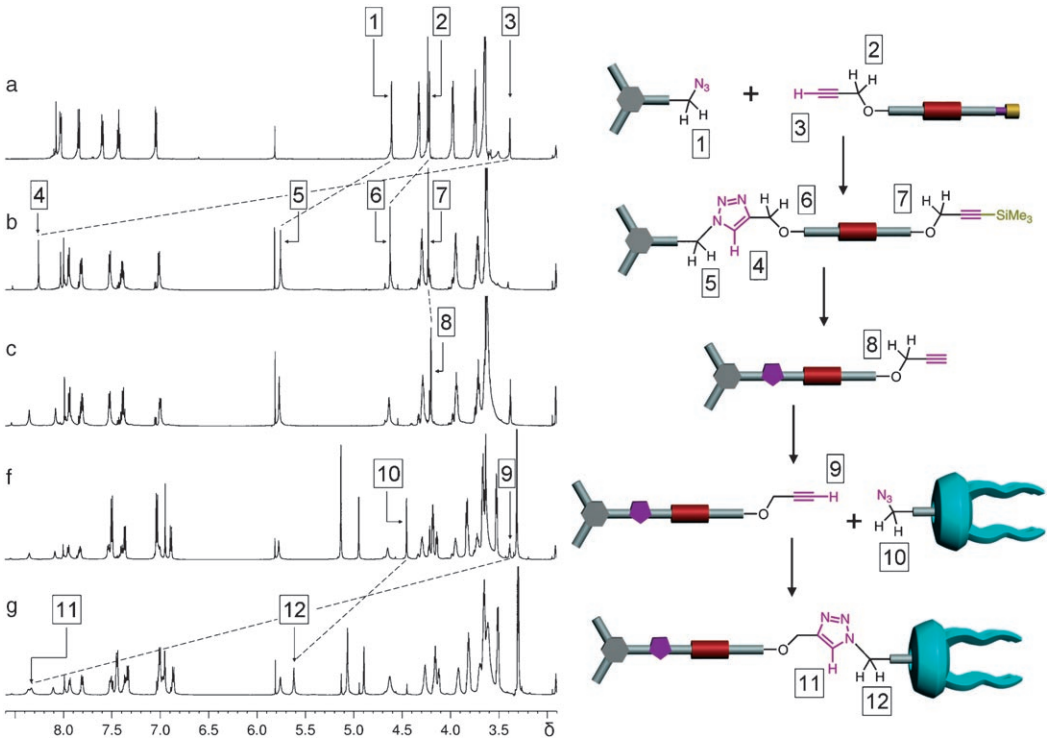

Figure 2. ^{1}H NMR (600 MHz, [D_7]DMF, 25°C) spectroscopic monitoring of the synthesis of the dumbbell compound **12**. Several diagnostic resonances are numbered and the changes monitored throughout the reaction steps indicated by letters **a**, **b**, **c**, **f**, **g** in Scheme 1. See the text for further discussion.

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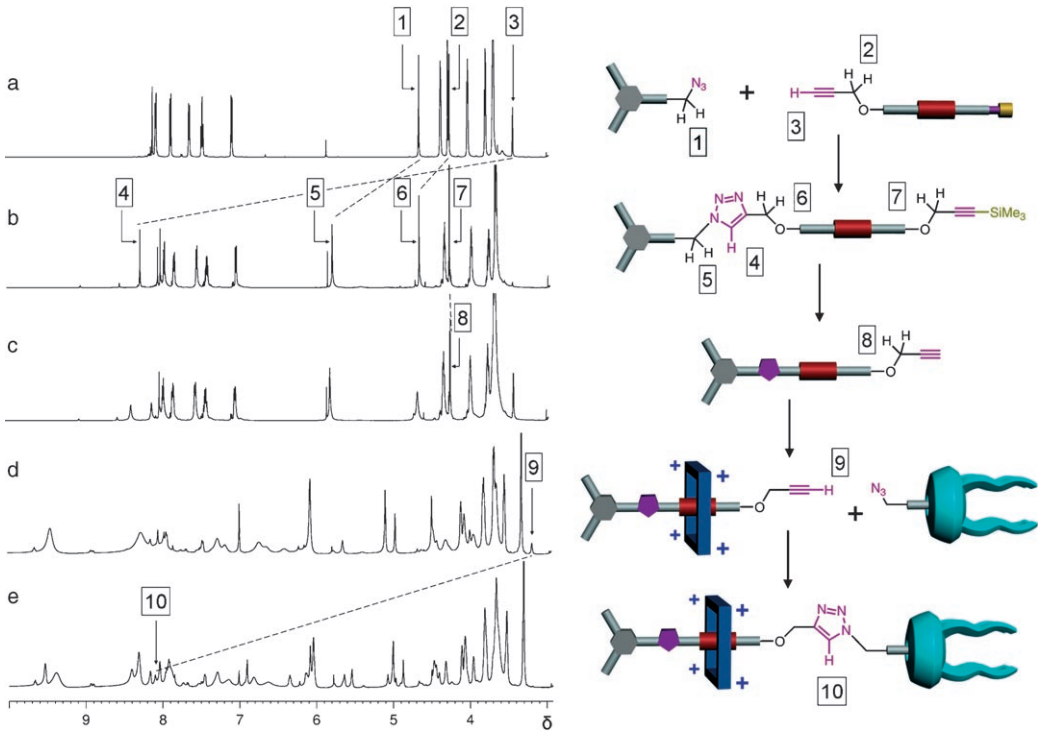

Figure 3. ^{1}H NMR (600 MHz, [D$_7$]DMF, 25 °C) spectroscopic monitoring of the synthesis of the [4]rotaxane **11**·12 PF_6. Several diagnostic resonances are numbered and the changes monitored throughout the reaction steps indicated by letters **a**, **b**, **c**, **d**, **e** in Scheme 1. See the text for further discussion.

in the formation of the [4]pseudorotaxane [**9**⊂3 **CBPQT**]·12 PF_6 which was stoppered with the monoazide **10** using the Cu-nanopowder/[Cu(MeCN)$_4$]PF_6-promoted CuAAC reaction to yield the amphiphilic branched [4]rotaxane **11**·12 PF_6. The addition of **CBPQT**·4 PF_6 caused broadening of all the peaks (Figure 3d) as a consequence of the many dynamic equilibria associated with the formation of pseudorotaxanes. The terminal alkyne proton resonance, however, was resolved clearly ($\delta = 3.17$ ppm) from the other signals and so it was used as a diagnostic resonance with which to monitor the progress of the final CuAAC reaction. The disappearance of the terminal alkyne proton resonance (Figure 3d) in the [4]pseudorotaxane [**9**⊂3 **CBPQT**]·12 PF_6 and the appearance of a second triazole peak ($\delta = 8.10$ ppm in Figure 3e) for the [4]rotaxane **11**·12 PF_6 heralded the completion of the second CuAAC reaction. Although we had never performed the second CuAAC reaction at low temperatures in the test-bed investigations (Table 2, entry 5), the tris-alkyne **9** was consumed completely during the final CuAAC reaction performed at −5 °C. All three of the second CuAAC reactions occurred with considerable efficiency, forming the three-fold symmetric amphiphilic [4]rotaxane in 44 % yield from a one-pot synthesis. Although, the isolated yield of **11**·12 PF_6 at first glance may seem low in comparison with the near-quantitative conversions observed by ^{1}H NMR spectroscopy, it represents the overall yield for a sum of nine "consecutive" reactions,[17] including the formation of three mechanical bonds, starting from no less than 10 building blocks. Also, extensive purification by preparative thin-layer chromatography was required in order to isolate the highly polar amphiphilic branched [4]rotaxane as a pure compound. In addition, a small quantity of a minor [2]rotaxane by-product, comprised of a **CBPQT**$^{4+}$-encircled thread **7**, stoppered by two hydrophilic stoppers **10**, was isolated. The formation of this compound can be attributed to the use of a very slight excess of **7** over **6** at the start of the three-step reaction sequence. Importantly, no evidence of constitutional defects—for example, missing rings, missing DNP threads, or crosslinking—was observed during the template-directed synthesis of **11**·12 PF_6. The successful silver-catalyzed silyl deprotection, performed in the second and intermediate step of the sequence, although not forming a bond itself, enabled the direction of the useful bond-forming CuAAC reaction in the third step of the sequence. Moreover, this reaction is another example that can be added to the small list of chemical reactions that may be performed in the presence of **CBPQT**$^{4+}$.

Conclusion

The protocol presented demonstrates the general and highly convergent nature of the sequential CuAAC strategy for the template-directed synthesis of a tripodal [4]rotaxane. Employing this one-pot methodology, constitutionally unsymmetrical rotaxanes may be prepared quickly and efficiently, aiding and abetting their continued use as components of molecular machinery and electronics. This methodology sets

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forth a new synthetic paradigm for **CBPQT**$^{4+}$-containing compounds in which the formation of the mechanical bond need not occur in the final step of the synthesis. These advances have been driven by the discovery and use of reactions amenable to the sensitive nature of **CBPQT**$^{4+}$. We intend to continue to develop new synthetic strategies performed under thermodynamic[18] as well as kinetic[2–4] control so that mechanical bonds may be precisely and predictably introduced into a wide range of complex functional molecules.

Experimental Section

General methods: All reagents were purchased from commercial suppliers (Aldrich or Fisher) and used without purification. Dry solvents were obtained from a commercial DriSolv solvent delivery system (EMD Chemicals). The molarity of *n*BuLi solutions was determined immediately before use by titration using salicyaldehyde phenylhydrazone[19] as an indicator. Cyclobis(paraquat-*p*-phenylene),[20] 1,5-bis[2-(2-{2-(2-propyne)ethoxy}ethoxy)ethoxy]naphthalene,[4b] and 3,4,5-tris-[{2-(2-methoxy)-ethoxy}ethoxybenzyloxy]benzyl chloride[9i] were prepared by using previously published procedures. Copper nanopowder was used as received from Aldrich and is described as metallic copper (99.8%) particles <100 nm in size. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} (E. Merck). Preparative thin layer chromatography (Prep TLC) was performed on glass plates with a 1 mm thick layer of silica gel 60 F_{254} (E. Merck). Column chromatography was performed on silica gel 60F (Merck 9385, 0.040–0.063 mm). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 600 (^{1}H: 600 MHz; ^{13}C: 150 MHz) or 500 (^{1}H: 500 MHz; ^{13}C: 126 MHz) spectrometer. Chemical shifts are reported as parts per million (ppm) downfield from the Me_4Si resonance as the internal standard for both ^{1}H and ^{13}C NMR spectroscopies. Electrospray ionization (ESI) mass spectra were measured on a Finnigan LCQ ion-trap mass spectrometer using 1:1 MeCN/H_2O as the mobile phase. High-resolution fast atom bombardment (HR-FAB) mass spectra were obtained on a JEOL JMS-600H high-resolution mass spectrometer equipped with a FAB probe. Electrospray ionization (EI) mass spectra were obtained on a Finnigan LCQ ion trap mass spectrometer.

Method development

General procedure for single-step methodology experiments and Table 1, entry 1: 3-Trimethylsilyl-2-propyn-1-ol (**1**) (0.010 g, 0.078 mmol) and 1-azidohexane (**3**) (0.010 g, 0.078 mmol) were dissolved in [D_7]DMF (0.780 mL) in an NMR tube. Stock solutions of $CuSO_4$·5H_2O in [D_7]DMF (18 μL, 0.072 M, 0.05 equiv per azide) and ascorbic acid in [D_7]DMF (18 μL, 0.144 M, 0.10 equiv per azide) were added and the mixture was left at room temperature. The reaction progress was monitored by comparing the integrated area of the disappearing -CH_2N$_3$ resonance at $\delta=3.50$ ppm with that of the appearing -CH_2N(triazole) at $\delta=$ 4.57 ppm in the ^{1}H NMR spectrum of the reaction mixture.

Methodology experiment for Table 1, entry 2: The above procedure was followed by using 3-trimethylsilyl-2-propyn-1-ol (**1**) (0.010 g, 0.078 mmol), 1-octyne (**2**) (0.0090 g, 0.078 mmol), and 1-azidohexane (**3**) (0.010 g, 0.078 mmol) dissolved in [D_7]DMF (0.780 mL) and stock solutions of $CuSO_4$·5H_2O in [D_7]DMF (18 μL, 0.072 M, 0.05 equiv per azide) and ascorbic acid in [D_7]DMF (18 μL, 0.144 M, 0.10 equiv per azide).

General procedure for two-step methodology experiments and Table 2, entry 1: 3-Trimethylsilyl-2-propyn-1-ol (**1**) (0.0070 g, 0.055 mmol) was dissolved in [D_7]DMF (0.546 mL) in an NMR tube. A stock solution of $AgPF_6$ in [D_7]DMF (30 μL, 0.1 M, 0.05 equiv per alkyne) and H_2O (3 μL, 0.164 mmol) were added and the mixture was left at room temperature. The reaction progress was monitored by comparing the integrated area of the disappearing -CH_2CCSi singlet resonance at $\delta=4.19$ ppm with that of the appearing -CH_2CCH doublet resonance at $\delta=4.16$ ppm in the ^{1}H NMR spectrum of the reaction mixture. Following sufficient conversion, to this solution was added 1-azidohexane (**3**) (0.0080 g, 0.060 mmol) and stock solutions of $CuSO_4$·5H_2O in [D_7]DMF (18 μL, 0.072 M, 0.05 equiv per azide) and ascorbic acid in [D_7]DMF (18 μL, 0.144 M, 0.10 equiv per azide) and the reaction was left at room temperature. Conversion of the CuAAC reaction was monitored by comparing the integrated area of the disappearing -CH_2N$_3$ resonance at $\delta=3.50$ ppm with that of the appearing -CH_2N(triazole) at $\delta=4.57$ ppm in the ^{1}H NMR spectrum of the reaction mixture.

Methodology experiment for Table 2, entry 2: The above procedure was followed by using 3-trimethylsilyl-2-propyn-1-ol (**1**) (0.0070 g, 0.055 mmol), [D_7]DMF (0.546 mL), stock solution of $AgPF_6$ in [D_7]DMF (30 μL, 0.10 M, 0.05 equiv per alkyne), H_2O (3 μL, 0.164 mmol), 1-azidohexane (**3**) (0.0080 g, 0.060 mmol), and copper nanopowder (0.0010 g, 0.016 mmol). The reaction mixture was heterogeneous, as the copper nanopowder remained at the bottom of the NMR tube.

Methodology experiment for Table 2, entry 3: The above procedure was followed using 3-trimethylsilyl-2-propyn-1-ol (**1**) (0.0080 g, 0.055 mmol), [D_7]DMF (0.530 mL), stock solution of $AgPF_6$ in [D_7]DMF (23.5 μL, 0.235 M, 0.1 equiv per alkyne), H_2O (3 μL, 0.16 mmol), 1-azidohexane (**3**) (0.0080 g, 0.060 mmol), and [$Cu(MeCN)_4$]PF_6 (0.002 g, 0.005 mmol, 0.1 equiv per alkyne). After the addition of the $AgPF_6$ solution, the mixture was warmed to 40 °C. The subsequent CuAAC reaction was performed at room temperature.

Methodology experiment for Table 2, entry 4: The above procedure was followed by using 3-trimethylsilyl-2-propyn-1-ol (**1**) (0.0070 g, 0.055 mmol), [D_7]DMF (0.546 mL), stock solution of $AgPF_6$ in [D_7]DMF (23.5 μL, 0.235 M, 0.1 equiv per alkyne), H_2O (3.0 μL, 0.16 mmol), 1-azidohexane (**3**) (0.0080 g, 0.060 mmol), copper nanopowder (0.0010 g, 0.016 mmol), and [$Cu(MeCN)_4$]PF_6 (0.002 g, 0.005 mmol, 0.1 equiv per alkyne). After the addition of the $AgPF_6$ solution, the mixture was warmed to 40 °C. The subsequent CuAAC reaction was performed at room temperature.

Methodology experiment for Table 2, entry 5: The above procedure was followed by using 3-trimethylsilyl-2-propyn-1-ol (**1**) (0.0070 g, 0.055 mmol), [D_7]DMF (0.546 mL), stock solution of $AgPF_6$ in [D_7]DMF (23.5 μL, 0.235 M, 0.1 equiv per alkyne), H_2O (3.0 μL, 0.16 mmol), 1-azidohexane (**3**) (0.0080 g, 0.060 mmol), copper nanopowder (0.0010 g, 0.016 mmol), [$Cu(MeCN)_4$]PF_6 (0.002 g, 0.005 mmol, 0.1 equiv per alkyne), and **CBPQT**·4PF_6 (0.0115 g, 0.0110 mmol, 0.2 equiv per alkyne). **CBPQT**·4PF_6 was dissolved initially with **1** and remained as a spectator throughout the sequence. After the addition of the $AgPF_6$ solution, the mixture was warmed to 40 °C. The subsequent CuAAC reaction was performed at room temperature.

Synthesis and characterization

1-[2-(2-{2-(3-Trimethylsilyl-2-propyne)ethoxy}ethoxy)ethoxy]-5-[2-(2-{2-(2-propyne)ethoxy}ethoxy)ethoxy]naphthalene (7): *n*BuLi (0.52 M in hexanes, 665 μL, 0.343 mmol) was added dropwise to a solution of 1,5-bis[2-(2-{2-(2-propyne)ethoxy}ethoxy)ethoxy]naphthalene,[4b] (0.156 g, 0.311 mmol) dissolved in dry THF (15.7 mL) at −78 °C under an Ar atmosphere. After stirring for 15 min at −78 °C Me_3SiCl (48.0 μL, 0.374 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 12 h. The crude reaction mixture was quenched with saturated aq. NH_4Cl (15 mL) and extracted with CH_2Cl_2 (4×20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated. The crude product was subjected to chromatography (SiO_2, 93:7 to 90:10 CH_2Cl_2/Et_2O eluent) to give **7** (47 mg, 26% yield) as a pale yellow oil. **7**: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): $\delta=7.86$ (d, ^3J(H,H) = 8 Hz, 2H, DNP aryl -H *p*-O), 7.34 (t, ^3J(H,H) = 8 Hz, 2H, DNP aryl -H *m*-O), 6.84 (d, ^3J(H,H) = 8 Hz, 2H, DNP aryl -H *o*-O), 4.30 (t, ^3J(H,H) = 5 Hz, 4H, DNP-OCH_2), 4.20 (s, 2H, -OCH_2CCSi), 4.19 (d, ^4J(H,H) = 2.4 Hz, 2H, -OCH_2CCH), 4.00 (t, ^3J-(H,H) = 5 Hz, 4H), 3.82–3.80 (m, 4H), 3.72–3.67 (m, 12H), 2.41 (t, ^4J-(H,H) = 2.4 Hz, 1H, -CCH), 0.17 ppm (s, 9H, -Si(CH_3)$_3$); ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C, TMS): $\delta=154.5$, 126.9, 125.2, 114.8, 105.8, 101.6, 91.5, 79.8, 74.6, 71.1, 70.9, 70.9, 70.6, 70.6, 70.0, 69.3, 69.2, 68.1, 59.3, 58.5, 0.0 ppm; HRMS (FAB): calcd for $C_{31}H_{44}O_8Si$: *m/z* 572.2805; found: *m/z* 572.2823.

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Tris-1,3,5-(4′-azidomethyl)benzene (6): NaN_3 (1.079 g, 16.61 mmol) was added to a solution of tris-1,3,5-(4′-chloromethyl)benzene, (0.500 g, 1.11 mmol) dissolved in dry DMF (75 mL) and the solution was stirred at 60 °C for 24 h. The crude reaction mixture was quenched with H_2O (75 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried ($MgSO_4$), and evaporated. The crude product was subjected to chromatography (SiO_2, 7:3 hexane/CH_2Cl_2) to give **5** (450 mg, 86% yield) as a white solid. **5**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.78 (s, 3H, central aryl-H), 7.73 (d, ^3J(H,H) = 8 Hz, 6H, aryl -H *m*-CH_2N_3), 7.45 (d, ^3J(H,H) = 8 Hz, 6H, aryl -H *o*-CH_2N_3), 4.42 ppm (s, 6H, CH_2N_3); ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C, TMS): δ = 141.8, 140.9, 134.8, 128.7, 127.7, 125.2, 54.5 ppm; HRMS (EI): calcd for $C_{27}H_{21}N_9$: *m/z* 471.1920; found: *m/z* 471.1939.

3,4,5-Tris[{2-(2-methoxy)ethoxy}ethoxybenzyloxy]benzyl azide (10): NaN_3 (0.379 g, 3.53 mmol) was added to a solution of 3,4,5-tris-[(2-(2-methoxy)ethoxy)ethoxybenzyloxy]benzyl chloride,[9i] (0.282 g, 0.353 mmol) dissolved in DMF (3.7 mL) and the solution was stirred at 60 °C for 24 h. The crude reaction mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were washed with H_2O (2×20 mL), brine (20 mL), dried ($MgSO_4$), and evaporated. The crude product was subjected to chromatography (SiO_2, EtOAc eluent) to give **10** (221 mg, 77% yield) as a pale yellow amorphous solid. **10**: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.32 (d, ^3J(H,H) = 9 Hz, 4H, aryl -H *m*-O), 7.27 (d, ^3J(H,H) = 9 Hz, 2H, aryl -H *m*-O), 6.91 (d, ^3J(H,H) = 9 Hz, 4H, aryl -H *o*-O), 6.79 (d, ^3J(H,H) = 9 Hz, 2H, aryl -H *o*-O), 6.57 (s, 2H, aryl -H *o*-CH_2N_3), 5.01 (s, 4H, benzylic CH_2O), 4.94 (s, 2H, benzylic CH_2O), 4.21 (s, 2H, -CH_2N_3), 4.16 (t, ^3J(H,H) = 5 Hz, 4H), 4.12 (t, ^3J(H,H) = 5 Hz, 2H), 3.89–3.85 (m, 6H), 3.74–3.71 (m, 6H), 3.60–3.57 (m, 6H), 3.40 (s, 6H, OCH_3), 3.39 ppm (s, 3H, OCH_3); ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C, TMS): δ = 158.7, 158.6, 153.2, 138.5, 130.9, 130.3, 130.2, 129.3, 129.2, 114.7, 114.3, 108.2, 74.7, 72.1, 71.2, 70.9, 70.8, 69.9, 67.6, 67.5, 59.2, 55.1 ppm; HRMS (FAB): calcd for $C_{43}H_{55}O_{12}N_3$(Na): *m/z* 828.3649; found: *m/z* 828.3684; elemental analysis: calcd: C 64.08, H 6.88, N 5.21; found: C 64.33, H 6.81, N 5.19.

[4]Rotaxane (11·12 PF_6): Tris-1,3,5-(4′-azidomethyl)benzene (**6**) (0.0107 g, 0.0227 mmol) and DNP derivative **7** (0.0390 g, 0.0682 mmol, 1.0 equiv per azide) were dissolved in [D_7]DMF (0.45 mL) in an NMR tube. Stock solutions of $CuSO_4$·5H_2O in [D_7]DMF (45 μL, 0.072 M, 0.05 equiv per azide) and ascorbic acid in [D_7]DMF (45 μL, 0.144 M, 0.10 equiv per azide) were added and the mixture left at room temperature for 20 h (until the -C$H_2$$N_3$ resonance at 4.61 ppm was replaced by the -CH_2N-(triazole) resonance at 5.76 ppm in the ^{1}H NMR spectrum of the reaction mixture). A stock solution of $AgPF_6$ in [D_7]DMF (50 μL, 0.235 M, 0.17 equiv per TMS) and H_2O (3.7 μL, 0.2081 mmol, 9 equiv per TMS) were added and the mixture left at 40 °C for 36 h (until the -CH_2CCSi singlet resonance at δ = 4.36 was replaced by the -CH_2CCH doublet resonance at δ = 4.23 ppm and the -CCSi(CH_3)$_3$ resonance at δ = 0.16 ppm was replaced by the -Si(CH_3)$_3$ resonances at δ = 0.08 and 0.05 ppm in the ^{1}H NMR spectrum of the reaction mixture). 3,4,5-Tris[{2-(2-methoxy)-ethoxy}ethoxybenzyloxy]benzyl azide (**10**) (0.0584 g, 0.0725 mmol, 1.1 equiv per alkyne), **CBPQT**·4PF_6 (0.0840 g, 0.0763 mmol, 1.1 equiv per DNP), Cu nanopowder (Aldrich, 0.002 g, 0.0315 mmol), and [Cu-(MeCN)$_4$]PF_6 (0.002 g, 0.0054 mmol) were then added and the dark purple reaction mixture was cooled to −5 °C for 40 h (until the -CCH resonance at δ = 3.17 ppm was no longer observed in the ^{1}H NMR), after which time a Ag mirror had formed on the walls of the NMR tube. The reaction mixture was filtered through a fritted funnel to remove residual solids and the solvent evaporated. The resulting purple oil was redissolved in Me_2CO and the [4]rotaxane was purified by preparative TLC using 50% MeOH/CH_2Cl_2 followed by 3% w/v NH_4PF_6 in Me_2CO followed by a 12:7:1 1 M NH_4Cl/MeOH/$MeNO_2$ mobile phases consecutively on one preparative TLC plate. The rotaxane product was recovered from the silica gel by washing with excess water, then Me_2CO, and finally a 4% w/v NH_4PF_6 solution in Me_2CO. The recovered material was then re-subjected to preparative TLC using a 12:7:1 1 M NH_4Cl/MeOH/$MeNO_2$ mobile phase. The rotaxane product was again recovered from the silica gel as before. The Me_2CO was concentrated to a minimum volume, and the product was precipitated from this solution through the addition of an excess of cold water. The [4]rotaxane **11**·12PF_6 was isolated as a purple solid (78 mg, 44% yield). **11**·12PF_6: ^{1}H NMR (600 MHz, CD_3COCD_3, 52 °C, TMS) (assignments verified by COSY and HMQC): δ = 9.08 (br s, 24H, α-**CBPQT**$^{4+}$), 8.19 (br s, 24H, phenylene-**CBPQT**$^{4+}$), 7.92 (s, 3H, central benzene aryl -H), 7.90 (d, ^3J(H,H) = 8 Hz, 6H, central aryl -H *m*-methylene triazole), 7.83 (s, 3H, triazole -H), 7.74 (s, 3H, triazole -H), 7.56 (br s, 24H, β-**CBPQT**$^{4+}$), 7.46 (d, ^3J(H,H) = 8 Hz, 6H, central aryl -H *o*-methylene triazole), 7.32 (d, ^3J(H,H) = 8 Hz, 12H, stopper aryl -H *m*-O), 7.28 (d, ^3J(H,H) = 8 Hz, 6H, stopper aryl -H *m*-O), 6.92 (d, ^3J(H,H) = 8 Hz, 12H, stopper aryl -H *o*-O), 6.83 (d, ^3J(H,H) = 8 Hz, 6H, stopper aryl -H *o*-O), 6.74 (s, 6H, stopper aryl -H *o*-methylene triazole), 6.41 (d, ^3J(H,H) = 8 Hz, 3H, DNP aryl -H *p*-O), 6.30 (d, ^3J(H,H) = 8 Hz, 3H, DNP aryl -H *o*-O), 6.16 (t, ^3J(H,H) = 8 Hz, 3H, DNP aryl -H *m*-O), 6.08 (t, ^3J(H,H) = 8 Hz, 3H, DNP aryl -H *m*-O), 5.96 (br s, 24H, **CBPQT**$^{4+}$ benzyl -H), 5.56 (s, 6H, central CH_2-triazole), 5.39 (s, 6H, stopper CH_2-triazole), 4.96 (s, 12H, stopper phenyl-OCH_2), 4.88 (s, 6H, stopper phenyl-OCH_2), 4.45–4.39 (m, 12H, DNP-OCH_2), 4.37 (s, 6H, OCH_2-triazole), 4.34 (s, 6H, OCH_2-triazole), 4.25–4.17 (m, 12H), 4.13 (t, ^3J(H,H) = 5 Hz, 12H, stopper aryl-OCH_2), 4.10 (t, ^3J (H,H) = 5 Hz, 6H, stopper aryl-OCH_2), 4.06–3.97 (m, 12H), 3.95–3.85 (m, 12H), 3.83–3.74 (m, 30H), 3.67–3.60 (m, 18H), 3.53–3.48 (m, 18H), 3.31–3.27 (m, 27H, stopper-OCH_3), 2.72 (d, ^3J(H,H) = 8 Hz, 3H, DNP aryl -H *p*-O), 2.68 ppm (d, ^3J(H,H) = 8 Hz, 3H, DNP aryl -H *p*-O); ^{13}C NMR (151 MHz, CD_3COCD_3, 2 °C, TMS): δ = 159.6, 153.6, 151.9, 145.9, 145.6, 145.2, 141.1, 138.1, 137.7, 136.8, 132.2, 132.0, 131.9, 131.1, 130.8, 130.4, 129.7, 129.6, 128.9, 128.6, 126.8, 126.6, 125.2, 125.1, 125.0, 115.0, 114.7, 109.0, 107.9, 104.9, 104.7, 75.1, 72.4, 72.4, 71.7, 71.3, 71.2, 71.0, 70.9, 70.7, 70.1, 69.7, 68.8, 68.1, 65.8, 65.7, 64.3, 64.2, 58.7, 54.1, 53.5 ppm; MS (ESI; MeOH/H_2O 1:1, 0.1% AcOH): *m/z*: 1777.4 [*M*−4PF_6]$^{4+}$, 1392.7 [*M*−5PF_6]$^{5+}$, 1136.5 [*M*−6PF_6]$^{6+}$, 953.4 [*M*−7PF_6]$^{7+}$, 816.2 [*M*−8PF_6]$^{8+}$.

Dumbbell Compound (12): Tris-1,3,5-(4′-azidomethyl)benzene (**6**) (0.0103 g, 0.0219 mmol) and DNP derivative **7** (0.0378 g, 0.0659 mmol, 1.0 equiv per azide) were dissolved in [D_7]DMF (0.45 mL) in an NMR tube. Stock solutions of $CuSO_4$·5H_2O in [D_7]DMF (43 μL, 0.072 M, 0.05 equiv per azide) and ascorbic acid in [D_7]DMF (43 μL, 0.144 M, 0.10 equiv per azide) were added and the reaction mixture was held at room temperature for 20 h (until the -C$H_2$$N_3$ resonance at δ = 4.61 ppm was replaced by the -CH_2N(triazole) resonance at δ = 5.76 ppm in the ^{1}H NMR spectrum of the reaction mixture). A stock solution of $AgPF_6$ in [D_7]DMF (50 μL, 0.235 M, 0.17 equiv per TMS) and H_2O (3.7 μL, 0.208 mmol, 9 equiv per TMS) were added and the mixture was heated to 40 °C for 36 h (until the -CH_2CCSi singlet resonance at δ = 4.36 was replaced by the -CH_2CCH doublet resonance at δ = 4.23 ppm and the -CCSi(CH_3)$_3$ resonance at δ = 0.16 ppm was replaced by the -Si(CH_3)$_3$ resonances at δ = 0.08 and 0.05 ppm in the ^{1}H NMR spectrum of the reaction mixture). 3,4,5-Tris-[{2-(2-methoxy)ethoxy}ethoxybenzyloxy]benzyl azide (**10**) (0.0584 g, 0.0725 mmol, 1.1 equiv per alkyne), Cu nanopowder (Aldrich, 0.002 g, 0.0315 mmol), and [Cu(MeCN)$_4$]PF_6 (0.002 g, 0.0054 mmol) were then added and the reaction mixture was allowed to rest at room temperature for 24 h (until the -CC*H* resonance at δ = 3.38 ppm was replaced by the -C*H*(triazole) at δ = 8.31 ppm in the ^{1}H NMR spectrum of the reaction mixture), after which time a Ag mirror had formed on the walls of the NMR tube. The reaction mixture was filtered through a fritted funnel to remove the residual solids and the solvent evaporated. The resulting brown oil was subjected to chromatography (SiO_2, 10:90 Me_2CO/CH_2Cl_2 followed by 10:90 MeOH/CH_2Cl_2 eluent) to give **12** (63.2 mg, 65% yield) as a colorless oil. **12**: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) (assignments verified by COSY and HMQC): δ = 7.84 (d, ^3J(H,H) = 8 Hz, 6H, DNP aryl -H *p*-O), 7.71 (s, 3H, central benzene aryl -*H*), 7.64 (d, ^3J(H,H) = 8 Hz, 6H, central aryl -H *m*-methylene triazole), 7.53 (s, 3H, triazole -H), 7.43 (s, 3H, triazole -H), 7.34 (d, ^3J(H,H) = 8 Hz, 6H, central aryl -H *o*-methylene triazole), 7.35–7.26 (m, 24H), 6.91 (d, ^3J(H,H) = 8 Hz, 12H, stopper aryl -H *o*-O), 6.81–6.79 (m, 12H, stopper aryl -H *o*-O and DNP aryl -H *o*-O), 6.53 (s, 6H, stopper aryl -H *o*-methylene triazole), 5.51 (s, 6H, tris-phenyl benzene-CH_2N), 5.33 (s, 6H, stopper phenyl-CH_2N), 4.96 (s, 12H, stopper O-CH_2-phenyl), 4.92 (s, 6H, stopper O-CH_2-phenyl), 4.67 (s, 6H, triazole-CH_2O), 4.67 (s, 6H, triazole-CH_2O), 4.26–4.23 (m, 12H, DNP-OCH_2), 4.15 (t, ^3J(H,H) = 5 Hz, 12H, stopper phenyl-OCH_2), 4.13 (t, ^3J(H,H) = 5 Hz, 6H, stopper phenyl-OCH_2), 3.97–3.94 (m, 12H), 3.89–3.85 (m,

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18H), 3.79–3.76 (m, 12H), 3.74–3.72 (m, 18H), 3.70–3.66 (m, 36H), 3.60–3.58 (m, 18H), 3.40 ppm (s, 27H, stopper -OCH_3); ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 158.6, 158.6, 154.3, 153.2, 145.7, 145.9, 141.7, 141.2, 138.7, 134.2, 130.2, 130.0, 129.9, 129.2, 129.0, 128.7, 127.9, 126.7, 125.3, 125.1, 122.6, 122.6, 114.6, 114.3, 108.0, 105.7, 74.7, 71.9, 71.1, 70.9, 70.7, 70.7, 70.6, 70.6, 69.8, 69.8, 67.9, 67.4, 67.4, 64.7, 64.7, 59.1, 54.2, 53.7$ ppm; MS (ESI; MeOH/H_2O 1:1, 0.1% AcOH): *m/z*: 1464.4 $[M+3H]^{3+}$, 1098.5 $[M+4H]^{4+}$, 879.2 $[M+5H]^{5+}$; HRMS (ESI; MeOH/H_2O 1:1, 0.1% AcOH): *m/z*: calcd for $[C_{240}H_{298}N_{18}O_{60}]^{4+}$: 1098.5220 $[M+4H]^{4+}$; found: 1098.5203.

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