

Efficient Templated Synthesis of Donor–Acceptor Rotaxanes Using Click Chemistry

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The discovery of highly efficient synthetic strategies for making electrochemically switchable, mechanically interlocked compounds will facilitate their continued development as components in molecular electronic devices¹ (MEDs) and nanoelectromechanical systems² (NEMS). Traditionally, such compounds, incorporating cyclobis(paraquat-*p*-phenylene) (CBPQT⁴⁺) as the π -accepting ring component, have been synthesized³ by “clipping” a partially formed CBPQT⁴⁺ ring (Figure 1a) around a dumbbell or ring containing π -electron-rich recognition sites. Although this synthetic strategy has found wide application,⁴ the moderate yield typical of the CBPQT⁴⁺ clipping reaction limits its practical value to the preparation of [2]rotaxanes and [2]catenanes. Herein, we describe an alternative synthetic approach (Figure 1b,c) to donor–acceptor rotaxanes—including previously inaccessible [3]- and [4]rotaxanes. Their synthesis relies upon the efficient stoppering of their pseudorotaxane precursors.

Motivated by the use of click chemistry⁵ in the synthesis of a variety of functional materials,^{6–8} including an example⁹ in which

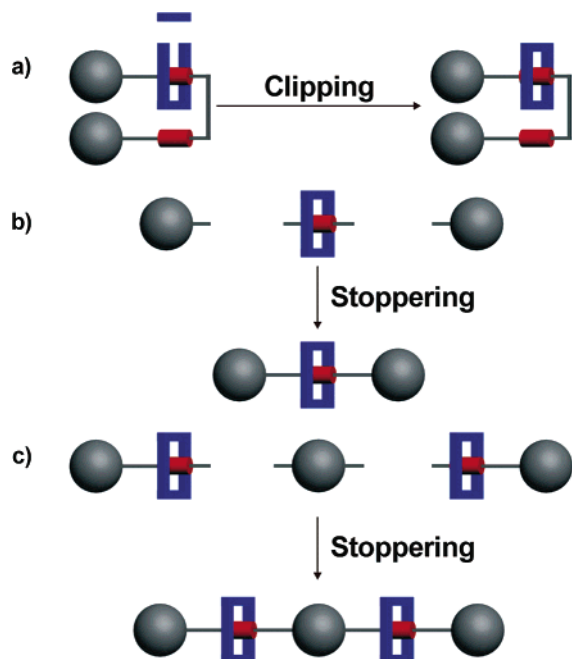
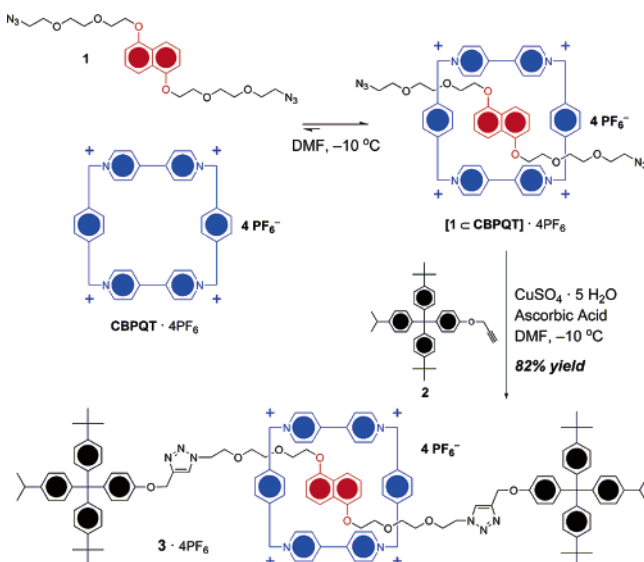


Figure 1. Graphical representations of different strategies employed in the template-directed syntheses of donor–acceptor rotaxanes: (a) clipping of a macrocycle around a dumbbell; (b) double stoppering of a pseudorotaxane to form a [2]rotaxane (Scheme 1); and (c) attachment of two semirotaxanes onto a bifunctional stopper to form a [3]rotaxane (Scheme 2). An analogous approach to a [4]rotaxane is depicted in Scheme 3.

Scheme 1



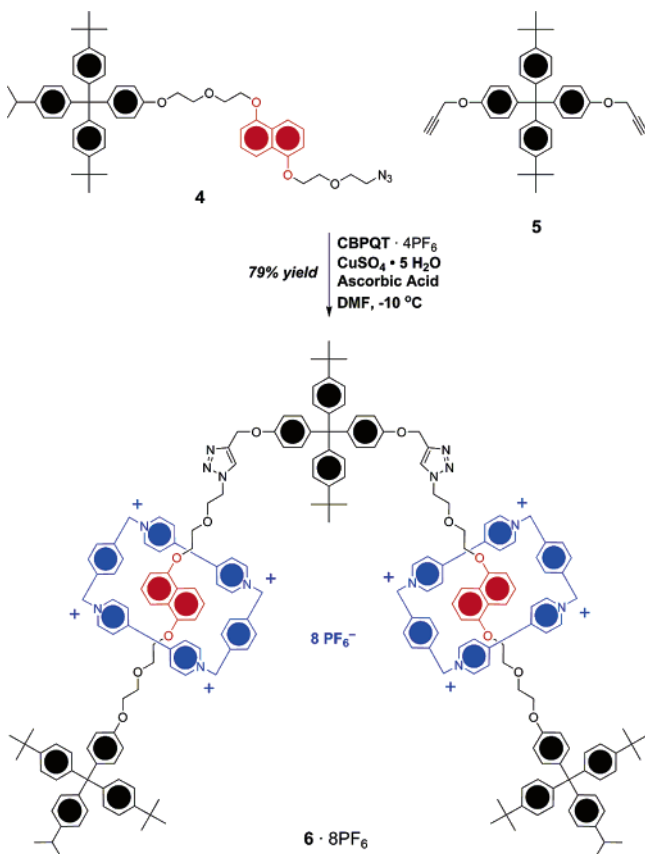
the Cu catalyst templates rotaxane formation, we reasoned that donor–acceptor rotaxanes might be obtained by attaching alkyne-terminated stoppers to CBPQT⁴⁺ pseudorotaxanes using the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (“click” chemistry). The click reaction has been noted for its high regioselectivity,^{5–8} tolerance of sensitive functional groups, mild reaction conditions,¹⁰ and excellent yields. The click reaction occurs at room temperature (and below), requiring only the addition of catalytic amounts of CuSO₄ and ascorbic acid, all conditions which are ideal for strong binding of CBPQT⁴⁺ to a wide variety of thread molecules containing π -donors.

This threading-followed-by-stopping approach is complementary to clipping and has a number of advantages. Because the recognition elements are fully formed from the outset of the reaction, templation utilizes the full thermodynamic binding of CBPQT⁴⁺ to the guest of interest. The click methodology is also much more convergent: relatively simple, modular rotaxane components are synthesized in parallel, and the mechanically interlocked structure is assembled in the final step of the reaction protocol. The general synthetic strategy (Scheme 1) involves the mixing of CBPQT·4PF₆ in DMF at –10 °C, with a 1,5-dioxynaphthalene (DNP) derivative **1** carrying azide-terminated glycol chains. Under these conditions, the equilibrium lies predominantly in favor of the [2]pseudorotaxane [**1** ⊂ CBPQT⁴⁺]·4PF₆. A propargyl ether-functionalized stopper **2** is then added to the reaction mixture along with CuSO₄·5H₂O and ascorbic acid. Following these mild reaction conditions, the [2]rotaxane **3**·4PF₆ was isolated in 82% yield. Formation of the dumbbell was not observed by thin layer chromatography.

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Scheme 2



Scheme 3

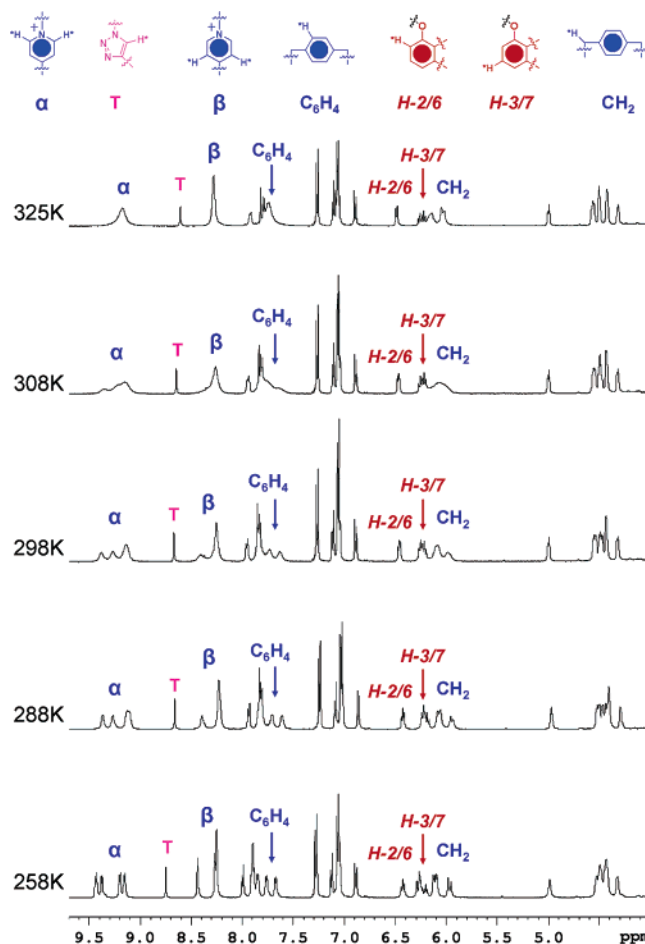
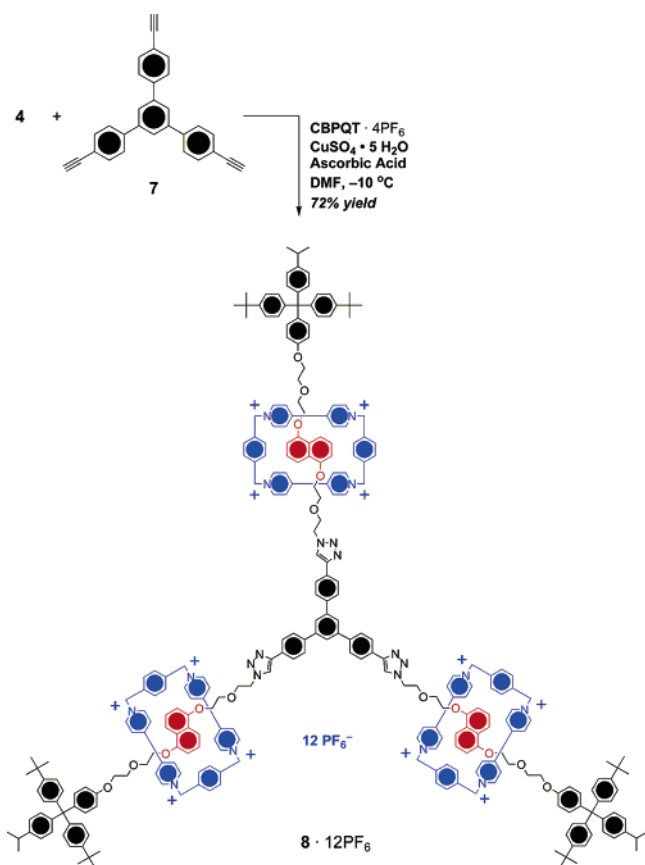


Figure 2. Partial ¹H NMR spectra (500 MHz, CD₃COCD₃) of 8·12PF₆ recorded at different temperatures. Several diagnostic peaks are labeled, including the signals for the CBPQT⁴⁺ α and β protons, and resonances for two of the three DNP protons. Slow rotation of the bipyridinium and *p*-phenylene units in the CBPQT⁴⁺ rings is reflected in their broad proton resonances at 298 K. At lower temperatures, these rotations are slowed even further until the signals become clearly resolved. The signals for the CBPQT⁴⁺ α and β protons coalesce into single, albeit broad, peaks at higher temperatures.

Encouraged by this successful proof of concept, we decided to apply this methodology to the synthesis of [3]rotaxanes. Doubly bistable [3]rotaxanes incorporating tethered CBPQT⁴⁺ rings have been used as redox-driven molecular muscles.¹¹ Although actuation was achieved, clipping two CBPQT⁴⁺ rings around the synthetically valuable palindromic dumbbell gave the desired [3]rotaxane in only 9% yield. Using the click methodology, a similar (albeit simplified) palindromic [3]rotaxane was synthesized from relatively simple precursors CBPQT·4PF₆, the stoppered DNP azide **4**, and bis(propargyl ether) **5** in 79% isolated yield.¹²

The comparative efficiency of the click methodology is emphasized by the synthesis (Scheme 3) of the branched [4]rotaxane 8·12PF₆ in 72% isolated yield after reacting **4** with tris-1,3,5-(4'-ethynylphenyl)benzene¹³ **7** in the presence of CBPQT·4PF₆. A clipping approach is expected to provide this [4]rotaxane in very low (<3%) yield.

The partial ¹H NMR spectra (Figure 2) of 8·12PF₆ reflect its 3-fold symmetry. The resonances for the DNP protons, which are shielded and resonate at δ = 6.49 (H-2/6), 6.22 (H-3/7), and 2.75 (H-4/8, not shown) ppm, are typical for rotaxanes containing CBPQT⁴⁺ and DNP residues. At +25 °C, rotations of the bipyridinium units and *p*-phenylene ring systems in the CBPQT⁴⁺ rings are slow on the ¹H NMR time scale, resulting in broadening

of the signals for the CBPQT⁴⁺ protons. The spectrum becomes much simpler as the signals for these protons coalesce at higher temperatures. At lower temperatures, the exchange processes between all of the relevant protons slow yet further, allowing for resolution of nonequivalent proton signals. Throughout the temperature range investigated, the triazole resonance remains a sharp singlet near $\delta = 8.60$ ppm, a reasonable value for triazole protons. This observation suggests that the triazole does not compete with DNP to bind with the CBPQT⁴⁺ ring—a hypothesis we are currently investigating more thoroughly.

During this preliminary research, it has become apparent that, as a result of using click chemistry as the covalent modification step in rotaxane synthesis, it not only renders the simple donor–acceptor [2]- and [3]rotaxanes (Schemes 1 and 2) much more accessible but it also provides the opportunity to prepare respectable quantities of more exotic mechanically interlocked compounds, such as the branched [4]rotaxane (Scheme 3). The synthesis and applications of these new materials to MEDs and NEMS will now become part of the ongoing research efforts in our laboratories.

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Supporting Information Available: Experimental details, spectral characterization data of all new compounds (PDF), and complete refs 1a,e and 11. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (a) Choi, J. W.; et al. *Chem.—Eur. J.* **2006**, *12*, 261. (b) Steurman, D. W.; Tseng, H.-R.; Peters, A. J.; Flood, A. H.; Jeppesen, J. O.; Nielsen, K. A.; Stoddart, J. F.; Heath, J. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6486. (c) Diehl, M. R.; Steurman, D. W.; Tseng, H.-R.; Vignon, S. A.; Star, A.; Celestre, P. C.; Stoddart, J. F.; Heath, J. R. *ChemPhysChem* **2003**, *4*, 1335. (d) Yu, H. B.; Luo, Y.; Beverly, K.; Stoddart, J. F.; Tseng, H.-R.; Heath, J. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 5706. (e) Luo, Y.; et al. *ChemPhysChem* **2002**, *3*, 519. (f) Collier, C. P.; Jeppesen, J. O.; Luo, Y.; Perkins, J.; Wong, E. W.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12632. (g) Collier, C. P.; Matternsteig, G.; Wong, E. W.; Luo, Y.; Beverly, K.; Sampaio, J.; Raymo, F. M.; Stoddart, J. F.; Heath, J. R. *Science* **2000**, *289*, 1172.
- (a) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348. (b) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines—A Journey into the Nano World*; Wiley-VCH: Weinheim, Germany, 2003. (c) Badjić, J. D.; Balzani, V.; Credi, A.; Silvi, S.; Stoddart, J. F. *Science* **2004**, *303*, 1845. (d) Collin, J.-P.; Heitz, V.; Sauvage, J.-P. *Top. Curr. Chem.* **2005**, *262*, 29. (e) Kay, E. R.; Leigh, D. A. *Top. Curr. Chem.* **2005**, *262*, 133. (f) Braunschweig, A. B.; Northrop, B. H.; Stoddart, J. F. *J. Mater. Chem.* **2006**, *16*, 32. (g) Moonen, N. N. P.; Flood, A. H.; Fernandez, J. M.; Stoddart, J. F. *Top. Curr. Chem.* **2005**, *262*, 99. (h) Tseng, H.-R.; Wu, D. M.; Fang, N. X. L.; Zhang, X.; Stoddart, J. F. *ChemPhysChem* **2004**, *5*, 111. (i) Tseng, H.-R.; Vignon, S. A.; Celestre, P. C.; Perkins, J.; Jeppesen, J. O.; Di Fabio, A.; Ballardini, R.; Gandolfi, M. T.; Venturi, M.; Balzani, V.; Stoddart, J. F. *Chem.—Eur. J.* **2004**, *10*, 155. (j) Stoddart, J. F. *Acc. Chem. Res.* **2001**, *34*, 410. (k) Balzani, V.; Gómez-López, M.; Stoddart, J. F. *Acc. Chem. Res.* **1998**, *31*, 405. (l) Ballardini, R.; Balzani, V.; Dehaen, W.; Dell'Erba, A. E.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *Eur. J. Org. Chem.* **2000**, 591. (m) Bermudez, V.; Capron, N.; Gase, T.; Gatti, F. G.; Kajzar, F.; Leigh, D. A.; Zerbetto, F.; Zhang, S. W. *Nature* **2000**, *406*, 608. (n) Berna, J.; Leigh, D. A.; Lubomska, M.; Mendoza, S. M.; Perez, E. M.; Rudolf, P.; Teobaldi, G.; Zerbetto, F. *Nat. Mater.* **2005**, *4*, 704. (o) Kern, J.-M.; Raehm, L.; Sauvage, J.-P.; Divisia-Blohorn, B.; Vidal, P. L. *Inorg. Chem.* **2000**, *39*, 1555. (p) Kinbara, K.; Aida, T. *Chem. Rev.* **2005**, *105*, 1377. (q) Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. *Chem. Rev.* **2005**, *105*, 1281. (r) Poleschak, I.; Kern, J.-M.; Sauvage, J.-P. *Chem. Commun.* **2004**, 474. (s) Raehm, L.; Kern, J.-M.; Sauvage, J.-P. *Chem.—Eur. J.* **1999**, *5*, 3310. (t) Karlen, S. D.; Garcia-Garibay, M. A. *Top. Curr. Chem.* **2005**, *102*, 10793. (u) Garcia-Garibay, M. A. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10771. (v) Perez, E. M.; Dryden, D. T. F.; Leigh, D. A.; Teobaldi, G.; Zerbetto, F. *J. Am. Chem. Soc.* **2004**, *126*, 12210. (w) Chatterjee, M. N.; Kay, E. R.; Leigh, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 4058. (x) Kelly, T. R. *Acc. Chem. Res.* **2001**, *34*, 514. (y) Fletcher, S. P.; Dumur, F.; Pollard, M. M.; Feringa, B. L. *Science* **2005**, *310*, 80.
- (a) Ashton, P. R.; Goodnow, T. T.; Kaifer, A. E.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1396. (b) Anelli, P.-L.; Spencer, N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 5131.
- (a) Philp, D.; Stoddart, J. F. *Synlett* **1991**, 445. (b) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725. (c) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1155. (d) Vignon, S. A.; Stoddart, J. F. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1493.
- (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
- (a) For examples of the click reaction for the synthesis of linear and diblock polymers, see: (a) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200. (b) Goodall, G. W.; Hayes, W. *Chem. Soc. Rev.* **2006**, *35*, 280. (c) Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4392. (d) Laurent, B. A.; Grayson, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 4238. (e) Riva, R.; Schmeits, P.; Stoffelbach, F.; Jerome, C.; Jerome, R.; Lecomte, P. *Chem. Commun.* **2005**, 5334. (f) Opsteen, J. A.; van Hest, J. C. M. *Chem. Commun.* **2005**, 57. (g) Lutz, J. F.; Börner, H. G.; Weichenhan, K. *Macromol. Rapid Commun.* **2005**, *26*, 514. (h) Ossipov, D. A.; Hilborn, J. *Macromolecules* **2006**, *39*, 1709.
- (a) For examples of the click reaction for the synthesis of dendrimers, see: (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928. (b) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. *Chem. Commun.* **2005**, 5775. (c) Malkoch, M.; Schleicher, K.; Drockenmüller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005**, *38*, 3663. (d) Lee, J. W.; Kim, B. K.; Kim, H. J.; Han, S. C.; Shin, W. S.; Jin, S. H. *Macromolecules* **2006**, *39*, 2418. (e) Lee, J. W.; Kim, J. H.; Kim, B. K.; Shin, W. S.; Jin, S. H. *Tetrahedron* **2006**, *62*, 894. (f) Fernandez-Megia, E.; Correa, J.; Rodriguez-Meizoso, I.; Riguera, R. *Macromolecules* **2006**, *39*, 2113.
- (a) For examples of grafting active functionalities along polymer chains, see: (a) Helms, B.; Mynar, J. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15020. (b) Mynar, J. L.; Choi, T. L.; Yoshida, M.; Kim, V.; Hawker, C. J.; Fréchet, J. M. J. *Chem. Commun.* **2005**, 5169. (c) Malkoch, M.; Thibault, R. J.; Drockenmüller, E.; Messerschmidt, M.; Voit, B.; Russell, T. P.; Hawker, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 14942. (d) O'Reilly, R. K.; Joralemon, M. J.; Wooley, K. L.; Hawker, C. J. *Chem. Mater.* **2005**, *17*, 5976.
- (a) Aucagne, V.; Hanni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186. (b) Previously, [2]- and [3]rotaxanes have been self-assembled from secondary dialkylammonium salts and crown ethers by using uncatalyzed Huisgen 1,3-dipolar cycloadditions to attach stoppers to the ends of the threads of [2]- and [3]pseudorotaxanes. See: Ashton, P. R.; Glink, P. T.; Stoddart, J. F.; Tasker, P. A.; White, A. J. P.; Williams, D. J. *Chem.—Eur. J.* **1996**, *2*, 729. Badjić, J. D.; Balzani, V.; Credi, A.; Lowe, J. N.; Silvi, S.; Stoddart, J. F. *Chem.—Eur. J.* **2004**, *10*, 1926.
- CBPQT⁴⁺·4PF₆ is sensitive to bases and nucleophilic conditions typically used in the synthesis of rotaxane dumbbells.
- Liu, Y.; et al. *J. Am. Chem. Soc.* **2005**, *127*, 9745.
- We anticipate that the production of bistable [3]rotaxanes will proceed equally smoothly simply by incorporating a second recognition site into the azide containing a half-dumbbell component.
- Simpson, C. D.; Matternsteig, G.; Martin, K.; Gherghel, L.; Bauer, R. E.; Rader, H. J.; Müllen, K. *J. Am. Chem. Soc.* **2004**, *126*, 3139.

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