Catenanes

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Synthesis of [2]Catenanes by Oxidative Intramolecular Diyne Coupling Mediated by Macrocyclic Copper(I) Complexes**

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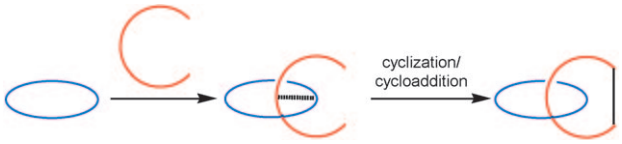
Mechanically interlocked compounds, such as catenanes and rotaxanes, are challenging synthetic targets which are expected to be important components of molecular machines[1] and switches.[2] Although catenanes were initially synthesized in low yields by the statistical approach[3] and the "directed" approach,[4] efficient synthesis of more complex molecules was achieved only when the components were preorganized by various interactions. Thus, a large number of catenanes were synthesized by the assembly of two or more components by template strategies. For example, Sauvage and co-workers achieved a high yield catenane synthesis by preorganization of the constituent parts as ligands around a Cu^{I} template.[5] The groups of Stoddart[6a,b] and Fujita[6c] applied π–π donor–acceptor interactions in very efficient syntheses of interlocked molecules. Hydrogen bonding was also utilized in the process of self-assembly by the groups of Vögtle[7a,b] and Leigh[7c] (Scheme 1). However, these methods

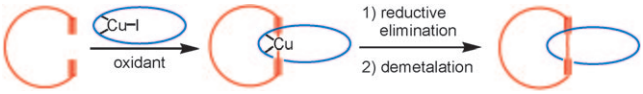


Scheme 1. Synthesis of catenanes by template method.

involve mutual interactions between the components and therefore the structures of the products are under many restrictions. The development of a new synthetic method would increase the availability of interlocked compounds and contribute to the progress of the study of molecular topology.

Recently, Leigh and co-workers reported a new method for the synthesis of rotaxanes,[8] utilizing catalytic reactions of macrocyclic Pd complexes to carry out bond-forming reactions inside the macrocycle. Only a catalytic amount of metal was required since the metal was transferred between the macrocyclic ligands. Our group,[9] as well as that of Leigh,[10] also reported the synthesis of rotaxanes by threading reactions of macrocyclic Cu complexes. In Leigh's system, a substoichiometric amount of the Cu species could be employed to isolate the rotaxanes in good yields.[11] A common notable feature of these reactions is that efficient threading was achieved by the reactions catalyzed (or mediated) by the macrocyclic complexes.

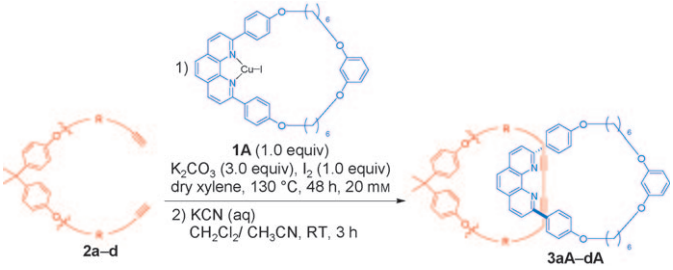
The successful synthesis of [2]rotaxanes by a threading reaction (Glaser coupling)[9] led us to study the synthesis of another important class of interlocked molecules, [2]catenanes. Herein, we report the first synthesis of [2]catenanes by the oxidative intramolecular homocoupling of α,ω-diynes with macrocyclic Cu^{I}–phenanthroline complexes (Scheme 2).

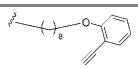
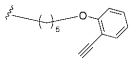
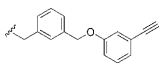
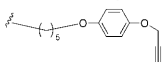


Scheme 2. Synthesis of [2]catenanes by the oxidative homocoupling of terminal diynes.

We synthesized a series of α,ω-diynes[12] with bisphenol A as a linker and examined the relationship between the structure of the diyne and the yield of the [2]catenanes in the presence of **1A**.[9] The results are summarized in Table 1.[13]

Table 1: Synthesis of [2]catenanes by intramolecular oxidative coupling of **2a–d**.



Entry	Diyne	Alkyne	Product	Yield [%]
1	**2a**		**3aA**	16
2	**2b**		**3bA**	18
3	**2c**		**3cA**	13
4	**2d**		**3dA**	trace

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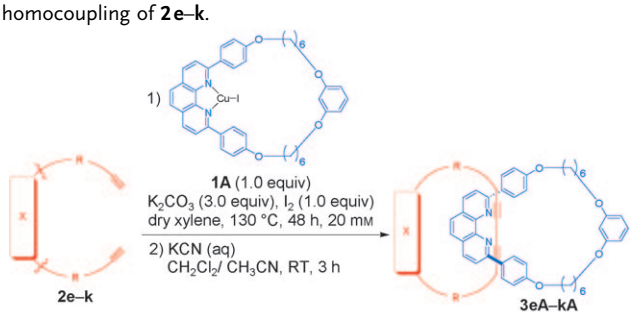
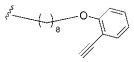
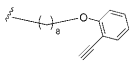
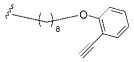
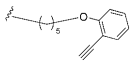
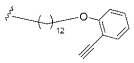
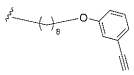
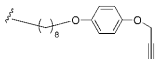
Most precursors reacted to give the desired [2]catenanes by the intramolecular coupling reaction. The α,ω-diynes with 2-alkoxyphenylacetylene moiety were good substrates for the synthesis of [2]catenanes, and the products were isolated in 16–18% yields (Table 1, entries 1 and 2). However, the yields of [2]catenanes decreased when other diynes were used as the substrates (Table 1, entries 3 and 4). Compound **2d** turned out to be an especially inferior substrate for the reaction (Table 1, entry 4). We assume that the yields of the products were influenced significantly by the conformation of the diynes. When the diynes were terminated with 2-alkoxyphenylacetylene moiety, the conformation of the substrate was more suitable for the formation of [2]catenanes, and the product was isolated in better yields.

Next, we synthesized α,ω-diynes[12] with different linkers and examined the relationship between the structure of the linker and the yield of [2]catenanes. The results are summarized in Table 2.

Table 2: Synthesis of [2]catenanes by the oxidative intramolecular homocoupling of **2e–k**.



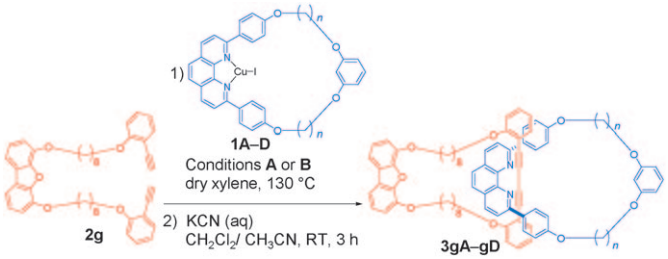
Entry	Diyne	Linker (X)	Alkyne	Product	Yield [%]
1	**2e**			**3eA**	13
2	**2f**			**3fA**	12
3	**2g**			**3gA**	27
4	**2h**			**3hA**	16
5	**2i**			**3iA**	10
6	**2j**			**3jA**	8
7	**2k**			**3kA**	trace

α,ω-Diynes linked with resorcinol, 4,5-dihydroxyxanthene, or 4,6-dihydroxydibenzofuran reacted with **1A** to give the corresponding [2]catenanes. Resorcinol (diyne **2e**, Table 2, entry 1) and 4,5-dihydroxyxanthene (diyne **2f**, Table 2, entry 2) were inferior linkers compared to that in **2a**, but 4,6-dihydroxydibenzofuran was a more successful linker moiety for the cyclization, and [2]catenane **3gA** was isolated in 27% yield (Table 2, entry 3). This result indicated that yields of the [2]catenanes might be influenced by the bond angle of the linkers. Thus, the two diyne units were preorganized in a favorable position for the intramolecular cyclization of **2h** (dibenzofuran linker) to proceed smoothly. Conversely, the angles in which other linkers preorganize the reacting diyne groups might be too small or too large.

Since 4,6-dihydroxydibenzofuran turned out to be the best linker, we synthesized α,ω-diynes with different spacers using 4,6-dihydroxydibenzofuran as a linker and they were utilized for the synthesis of catenanes, but diynes with shorter or longer spacers both resulted in decreased catenane yields (Table 2, entries 4 and 5). α,ω-Diynes terminated with different alkyne groups were also inferior substrates for the synthesis of [2]catenanes, affording very low yields (Table 2, entries 6 and 7). The desired intramolecular cyclization of the diynes competes with intermolecular oligomerization reactions, suggesting that diynes **2h–k** would not adopt a favorable conformation for the intramolecular coupling.

Finally, we examined the relationship between the size of the metal-coordinated macrocycle and the yield of the [2]catenanes, by carrying out the reaction using phenanthroline-based macrocycles with linker moieties of different lengths. The results are summarized in Table 3.

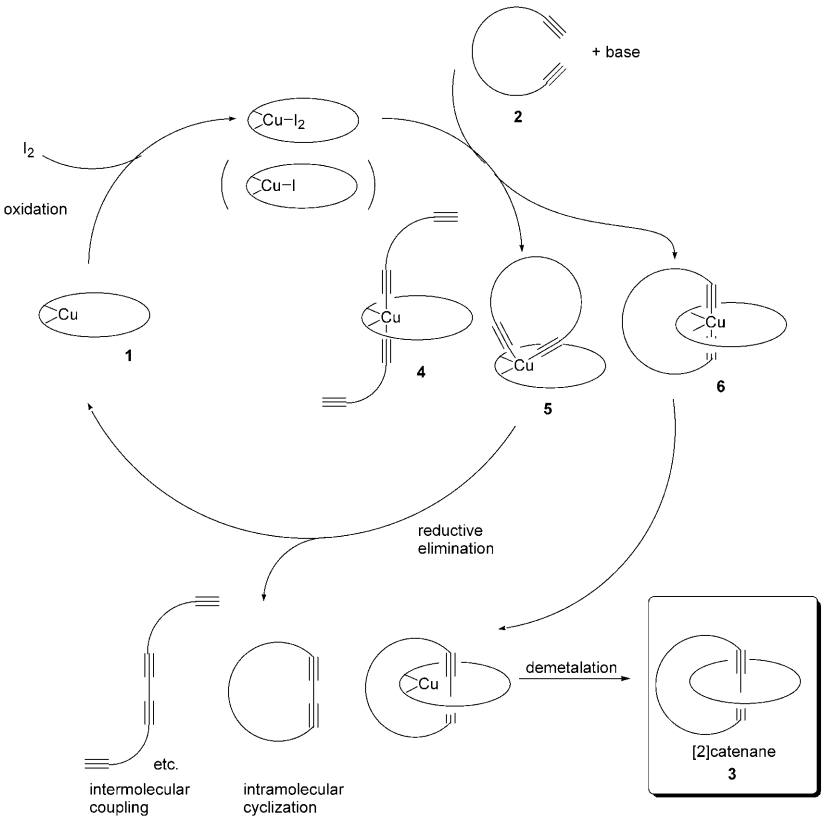
Table 3: Relationship between the ring size of the phenanthroline-based macrocycle and the yield of [2]catenanes.



Entry	Cu complex	Conditions[a]	Product	Yield [%]
1	**1A** ($n=6$)	A	**3gA**	27
2	**1B** ($n=8$)	A	**3gB**	26
3	**1C** ($n=10$)	A	**3gC**	9
4	**1D** ($n=12$)	A	**3gD**	9
5	**1A**	B	**3gA**	64
6	**1B**	B	**3gB**	58
7	**1C**	B	**3gC**	27
8	**1D**	B	**3gD**	34

[a] Conditions A: diyne (1.0 equiv), K_2CO_3 (3.0 equiv), I_2 (1.0 equiv), 48 h. Conditions B: diyne (5.0 equiv), K_2CO_3 (15.0 equiv), I_2 (5.0 equiv), 6 days.

When Cu^I complexes of smaller macrocycles ($n=6$, $n=8$) were treated with diyne **2g**, the resultant [2]catenanes were isolated in 26–27% yields (Table 3, entries 1 and 2). The yields of the catenanes decreased when Cu^I complexes of larger macrocycles ($n=10$, $n=12$) were used as the substrates (Table 3, entries 3 and 4). Owing to the increased flexibility of the larger complexes the favorable conformation for catenane formation is not retained. Nonetheless, it is possible to improve the yields by exploiting the "catalytic" nature of the reaction. Thus, by using 5 equivalents of **2g** as the substrate,



Scheme 3. Proposed mechanism for the formation of [2]catenanes.

we isolated catenane **3gA** in 64% yield. Similarly, [2]catenanes **3gB**, **3gC**, **3gD** were isolated in 58, 27 and 34% yields, respectively (Table 3, entries 6, 7 and 8). The improved yields of the catenanes in the presence of a large amount of the diynes can be reasonably explained by supposing that the Cu complex was regenerated when the catenane forming reaction failed (Scheme 3). Thus, the reaction of the diyne with the Cu-phenanthroline complex might proceed to give various intermediates, such as dialkynyl complex **4**,[14] spiro complex **5**, and pseudocatenane complex **6**. The [2]catenane would be isolated from **6** on reductive elimination. If, however, other complexes were formed, the Cu complex would be regenerated by the reductive elimination of the diyne and reoxidation by iodine. This "catalytic cycle" would continue until the diyne was consumed or the Cu complex was completely converted into the [2]catenane.[15,16]

The partial ^{1}H NMR spectra of **1A**, **3gA**, and a cyclic diyne are shown in Figure 1. As a result of the interaction between the components, the spectrum of **3gA** was different from those of the components. For example, the signals corresponding to the phenanthroline moiety of **1A** were at $\delta = 7.70$ and 7.32 ppm, whereas those of **3gA** were at $\delta = 8.06$ and 7.62 ppm, respectively. Compared to the signals of **1A**, many signals were shifted downfield in the spectrum of the catenane (**3gA**), in contrast to the tendency for [2]rotaxanes with similar structural features.[9]

In summary, we developed a novel approach for the synthesis of [2]catenanes by the reactions mediated by the macrocyclic Cu-phenanthroline complexes. The study revealed that a new class of [2]catenanes is accessible by utilizing bond-forming reactions catalyzed by the macrocyclic complexes. Further studies directed toward the synthesis of complex interlocked structures are ongoing.

Experimental Section

Synthesis of [2]catenane **3gA**: I_2 (5.1 mg, 0.020 mmol) was added with stirring to a mixture of macrocyclic phenanthroline–copper(I) complex **1A**[9] (16.6 mg, 0.020 mmol), diyne **3g** (13.2 mg, 0.020 mmol) and K_2CO_3 (8.4 mg, 0.060 mmol) in dry xylene (1.0 mL). The mixture was heated to 130 °C and stirred at this temperature for 48 h. After the mixture had cooled to room temperature, CH_3CN (2 mL), CH_2Cl_2 (2 mL), KCN (10 mg) and H_2O (1 mL) were added and the resulting mixture was stirred at room temperature for 3 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/CH_2Cl_2 (1:1 v/v) as eluent, and then further purified by gel permeation chromatography using $CHCl_3$ to yield [2]catenane **3gA** (6.9 mg, 27%) as a yellow amorphous solid. ^{1}H NMR (600 MHz, C_6D_6): $\delta = 8.91$–8.90 (d, $J = 7.8$ Hz, 4H), 8.14–8.12 (d, $J = 8.4$ Hz, 2H), 7.99–7.98 (d, $J = 8.4$ Hz, 2H), 7.71–7.69 (d, $J = 7.8$ Hz, 2H), 7.62 (s, 2H), 7.53–7.51 (dd, $J = 7.8$, 1.2 Hz, 2H), 7.27–7.23 (m, 6H), 7.20–7.18 (m, 2H), 6.92–6.89 (m, 2H), 6.77–6.76 (d, $J = 8.4$ Hz, 2H), 6.74–6.72 (dd, $J = 8.4$, 2.4 Hz, 2H), 6.61–6.59 (t, $J = 7.2$ Hz, 2H), 6.37–6.36 (d, $J = 8.4$ Hz, 2H), 3.98–3.96 (t, $J = 6.6$ Hz, 4H), 3.85–3.83 (t, $J = 6.0$ Hz, 4H), 3.66–3.63 (t, $J = 7.8$ Hz, 4H), 3.53–3.50 (t, $J = 7.2$ Hz, 4H), 1.65–1.52 (m, 12H), 1.42–1.40 (m, 4H), 1.23–1.18 (m, 4H), 1.16–1.10 (m, 8H), 0.82 (m, 4H), 0.70 ppm (m, 8H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 161.5$, 161.3, 161.0, 156.2, 147.0, 146.1, 137.0, 135.1, 132.3, 130.6, 130.4, 129.7, 129.6, 128.4, 128.3,127.5, 126.6,

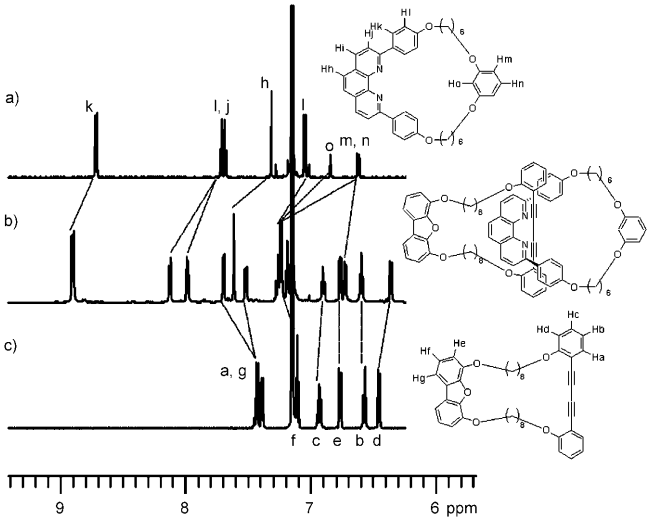


Figure 1. ^{1}H NMR spectra (600 MHz, C_6D_6) of a) macrocyclic phenanthroline (**1A**), b) [2]catenane (**3gA**), and c) a cyclic diyne.

125.9, 124.1, 120.3, 119.0, 115.3, 113.0, 112.0, 111.9, 110.8, 107.9, 101.5, 80.2, 79.1, 69.5, 68.7, 68.1, 67.7, 30.2, 29.93, 29.91, 29.7, 29.5, 29.2, 28.9, 26.8, 26.1, 26.0, 25.8 ppm; IR (KBr): $\tilde{\nu}$ = 2927, 2854, 1594, 1488, 1277, 1249, 1175, 1015, 838, 750 cm^{-1}; HR-MS calcd for $C_{86}H_{88}N_2O_9$: 1315.6382; found: 1315.6383.

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Keywords: catenanes · C–C coupling · copper · macrocycles · NMR spectroscopy

[1] a) V. Serreli, C. F. Lee, E. R. Key, D. A. Leigh, *Nature* **2007**, *445*, 523 – 527; b) V. Balzani, A. Credi, B. Ferrer, S. Silvi, M. Venturi, *Top. Curr. Chem.* **2005**, *262*, 1 – 27; c) C. P. Mandl, B. König, *Angew. Chem.* **2004**, *116*, 1650 – 1652; *Angew. Chem. Int. Ed.* **2004**, *43*, 1622 – 1624; d) J. V. Hernandez, E. R. Key, D. A. Leigh, *Science* **2004**, *306*, 1532 – 1537.

[2] a) S. Bonnet, J. P. Collin, M. Koizumi, P. Mobian, J. P. Sauvage, *Adv. Mater.* **2006**, *18*, 1239 – 1250; b) J. E. Green, J. W. Choi, A. Boukai, Y. Bunimovich, E. Johonston-Halperin, E. Delonno, Y. Luo, B. A. Sheri ff, K. Xu, Y. S. Shin, H. R. Tseng, J. F. Stoddart, J. R. Health, *Nature* **2007**, *445*, 414 – 417; c) A. H. Flood, J. F. Stoddart, J. R. Health, *Science* **2004**, *306*, 2055 – 2056; d) *Molecular Switches* (Eds.: B. L. Feringa), Wiley-VCH, Weinheim, **2001**.

[3] E. J. Wasserman, *J. Am. Chem. Soc.* **1960**, *82*, 4433 – 4434.

[4] a) G. Schill, C. Zürcher, *Angew. Chem.* **1969**, *81*, 996 – 997; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 988 – 988; b) G. Schill, E. Logemam, W. Vetter, *Angew. Chem.* **1972**, *84*, 1144 – 1145; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 1089 – 1090; c) For review, see, G. Schill in *Catenanes, Rotaxanes, and Knots* (Eds: A. T. Blomquist), Academic Press, New York, **1971**.

[5] a) C. O. Dietrich-Buchecker, J. P. Sauvage, J. P. Kintzinger, *Tetrahedron Lett.* **1983**, *24*, 5095 – 5098; b) C. O. Dietrich-Buchecker, J. P. Sauvage, *Chem. Rev.* **1987**, *87*, 795 – 810.

[6] a) F. M. Raymo, J. F. Stoddart, *Chem. Rev.* **1999**, *99*, 1643 – 1663; b) T. Ikeda, S. Saha, I. Aprahamian, K. C. F. Leung, A. Williams, W. Q. Deng, A. H. Flood, W. A. Goddart, J. F. Stoddart, *Chem. Asian J.* **2007**, *2*, 76 – 93; c) M. Fujita, F. Ibukuro, H. Hagihara, K. Ogura, *Nature* **1994**, *367*, 720 – 723.

[7] a) C. A. Schalley, W. Reckien, S. Peyerimhoff, B. Baytekin, F. Vögtle, *Chem. Eur. J.* **2004**, *10*, 4777 – 4789; b) F. Vögtle, S. Meier, R. Hoss, *Angew. Chem.* **1992**, *104*, 1628 – 1631; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1619; c) A. M. L. Fuller, D. A. Leigh, P. J. Lusby, A. M. Z. Slawin, D. B. Walker, *J. Am. Chem. Soc.* **2005**, *127*, 12612 – 12619.

[8] J. Berná, J. D. Crowley, S. M. Goldup, K. D. Hänni, A. L. Lee, D. A. Leigh, *Angew. Chem.* **2007**, *119*, 5811 – 5815; *Angew. Chem. Int. Ed.* **2007**, *46*, 5709 – 5713.

[9] S. Saito, E. Takahashi, K. Nakazono, *Org. Lett.* **2006**, *8*, 5133 – 5136.

[10] V. Aucagne, K. D. Hänni, D. A. Leigh, P. J. Lusby, D. B. Walker, *J. Am. Chem. Soc.* **2006**, *128*, 2186 – 2187.

[11] V. Aucagne, J. Berná, J. D. Crowely, S. M. Goldup, K. D. Hänni, D. A. Leigh, P. J. Lusby, V. E. Ronaldson, A. M. Z. Slawin, A. Viterisi, D. B. Walker, *J. Am. Chem. Soc.* **2007**, *129*, 11950 – 11963.

[12] See the Supporting Information.

[13] At the same time, we examined the cyclization of **2** in the presence of an acyclic phenanthroline Cu complex. No correlation was evident between the yield of the cyclized product and the yield of the catenane.

[14] T. C. Higgs, S. Parsons, P. J. Bailey, A. C. Jones, F. McLachlan, A. Parkin, A. Dawson, P. A. Tasker, *Organometallics* **2002**, *21*, 5692 – 5702.

[15] The precise structure of the intermediate of this reaction is not clear, and Cu^{I}/Cu^{III} interconversion could be another possibility. The final important intermediate, however, should be a monomeric dialkynyl Cu species. The dimeric Cu complex which is postulated in some reactions would not form as an intermediate for this reaction. See, a) J. Berná, S. M. Goldup, A. L. Lee, D. A. Leigh, M. D. Symes, G. Teobaldi, F. Zerbetto, *Angew. Chem.* **2008**, *120*, 4464 – 4468; *Angew. Chem. Int. Ed.* **2008**, *47*, 4392 – 4396; b) W. Y. Lo, C.-H. Lam, V. W. W. Yam, N. Zhu, K. K. Cheung, S. Fathallaf, S. Messaoudi, B. L. Guennic, S. Kahlal, J. F. Halet, *J. Am. Chem. Soc.* **2004**, *126*, 7300 – 7310; c) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740 – 2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632 – 2657.

[16] The macrocyclic Cu complexes used in this study are efficient catalysts for the oxidative coupling of small alkynes such as 4-methoxyphenylacetylene and the coupling product was isolated in more than 90% yield in the presence of a catalytic amount (10 mol%) of the complex. Therefore, in principle, the reaction of a molecule of **1** would proceed with more than two molecules of the diyne, and a multicatenane could be isolated. However, we could not isolate a multicatenane from the reaction mixture. The study directed toward the formation of the multicatenane is ongoing.

