ChemComm

Scalable Synthesis of a [8]Cycloparaphenyleneacetylene Carbon Nanohoop Using Alkyne Metathesis

Journal:	*ChemComm*
Manuscript ID	CC-COM-08-2021-004776.R1
Article Type:	Communication

COMMUNICATION

Scalable Synthesis of a [8]Cycloparaphenyleneacetylene Carbon Nanohoop Using Alkyne Metathesis

Received 00th January 20xx,
Accepted 00th January 20xx

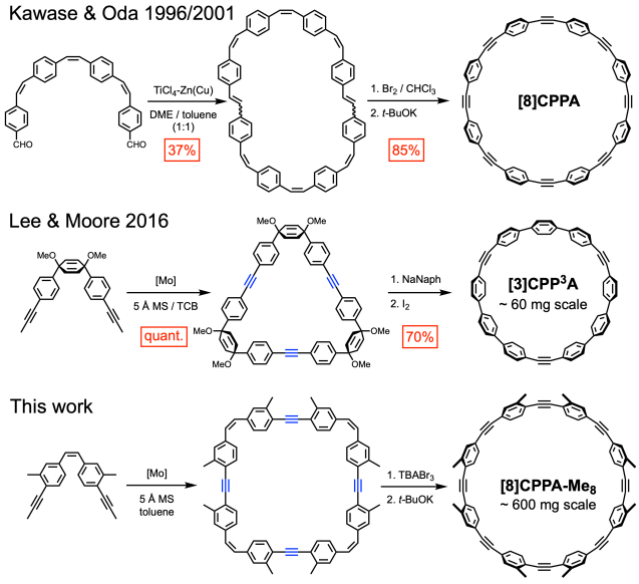
DOI: 10.1039/x0xx00000x

Xin Zhou,[a] Hyejin Kwon,[b] Richard R. Thompson,[a] Robert J. Herman,[a] Frank R. Fronczek,[a] Carson J. Bruns,[b,c] and Semin Lee[a]*

Large scale synthesis of cycloparaphenyleneacetylenes has been challenging due to low macrocyclization yields and harsh aromatization methods that often decompose strained alkynes. Herein, a *cis*-stilbene-based building block is subjected to alkyne metathesis macrocylization. The following sequence of alkene-selective bromination and dehydrobromination afforded a [8]cycloparaphenyleneacetylene derivative in high yield with good scalability. X-ray crystal structure and computational analysis revealed a unique same-rim conformation for the eight methyl groups on the nanohoop.

The successful synthesis of cycloparaphenylene (CPP) macrocycles by Jasti,[1] Itami,[2] and Yamago[3] prompted vast amounts carbon nanohoops[4] research. Myriad CPP derivatives with various aryl groups and diameters[5] have been reported since their emergence. Furthermore, improved synthetic methods[6, 7] and gram-scale syntheses[8-11] of CPPs allowed researchers to explore their molecular topologies,[12] supramolecular complexes,[11, 13] as well as their electronic,[14] biological,[15] and materials applications.[16] While great focus has been dedicated to CPPs, cycloparaphenyleneacetylenes (CPPA) have received relatively less attention due to their instability and poor scalability. The first CPPA was synthesized by Kawase and Oda in 1996 (Scheme 1)[17, 18] by implementing McMurry coupling for macrocyclization and converting the alkenes to alkynes via sequential bromination and dehydrobromination. However, the macrocyclization was often the yield-limiting step since ring size could not be easily controlled, requiring meticulous separation. In recent years, CPPAs have garnered more attention[19] due to their supramolecular assemblies[20] and chemical reactivities stemming from their strained alkynes.[21-23]

Recently, alternative methods for preparing CPPA derivatives have been reported. Miki and Ohe[24] used a series of Sonogashira coupling reactions to construct various triangular arylene-acetylene macrocycles (15–35% yield), which were subjected to reductive aromatization using H_2SnCl_4 or $SnCl_2$ to give several CPPA derivatives in good yields (27–87%). Jasti[23] and co-workers utilized a high-yielding (66–76%), gram-scale Pd-catalyzed aryl-aryl coupling reaction to prepare triangular macrocycles. The final desilylation and aromatization (H_2SnCl_4) resulted in carbon nanohoops with single strained alkynes. They were able to demonstrate strain-promoted azide-alkyne cycloadditions[21] (SPAAC) with benzyl azide and [2+2]cycloaddition–retrocyclization with tetracyanoethylene (TCNE).[25] On the other hand, Lee and Moore[22] used Mo(VI)-catalyzed alkyne metathesis[26-31] to synthesize a triangular macrocycle in gram-scale with a near-quantitative yield. The



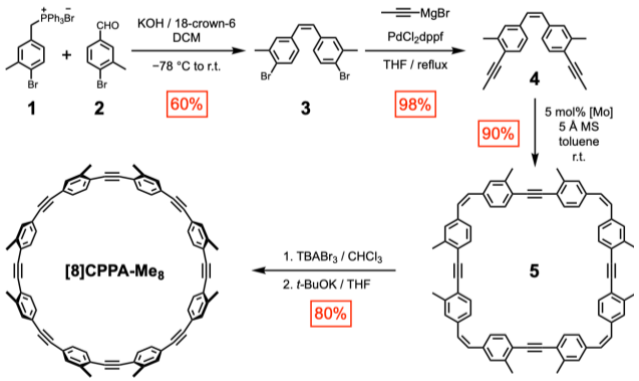
Scheme 1. Syntheses of CPPA derivatives.

[a] *Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70810, United States. Email: seminlee@lsu.edu*
[b] *College of Engineering and Applied Science, University of Colorado Boulder, Boulder, Colorado 80309, United States. Email: carson.bruns@colorado.edu*
[c] *ATLAS Institute, University of Colorado, Boulder, Colorado 80309, United States*

† Electronic Supplementary Information (ESI) available: Synthetic procedures, characterization, spectroscopic data of compounds. Computational conformation analysis and Cartesian coordinates of all calculated species. X-ray crystallographic data of **[8]CPPA-Me$_8$** (CCDC 2101753). See DOI: 10.1039/x0xx00000x

following reductive aromatization using sodium naphthalenide (NaNaph) resulted in **[3]CPP^{3}A** in high yield (70%). **[3]CPP^{3}A** was able to undergo three SPAAC reactions with an azido compound. Later, Zhou and Lee[32] synthesized larger **[3]CPP^{4}A** and **[3]CPP^{5}A** using similar methods in good yield (85–88%).

We note that the CPPA syntheses mentioned above have not demonstrated reductive aromatization in a scalable manner beyond 100 mg per reaction. For instance, aromatization using NaNaph to synthesize **[3]CPP^{n}A** (n = 3, 4, 5) resulted large amounts of insoluble byproducts when the reaction was performed with more than 100 mg of the triangular macrocycle. Dadley[33] and Levin[34, 35] have previously reported that diphenylacetylene derivatives can be reduced to radical anions that further convert into stilbene derivatives under strong



Scheme 2. Synthesis of **[8]CPPA-Me$_8$** carbon nanohoop.[a]

[a][Mo]: tris(*tert*-butyl(3,5-dimethylphenyl)amino)(propylidyne) molybdenum(VI) with 6 equivalents of Ph_3SiOH.

reducing conditions. Unfortunately, the alternative aromatization method developed by Yamago[6] using H_2SnCl_4 failed to give the desired **[3]CPP^{4}A** and **[3]CPP^{5}A** compounds.[32] Therefore, we decided to forgo reductive aromatization, rather combining the benefits of alkyne metathesis with Kawase and Oda's bromination/dehydrobromination to achieve a scalable synthetic method to prepare CPPA derivatives.

A *cis*-stilbene-based dipropynyl building block (**4**, Scheme 2) was designed for four reasons: (i) The bent angle of *cis*-stilbene facilitates macrocyclization. (ii) Alkenes are known to be orthogonal to Mo(VI)-catalyzed alkyne metathesis. Therefore, they are unlikely to react during macrocyclization. (iii) The alkene can be converted to a strained alkyne using sequential bromination/dehydrobromination. (iv) The two methyl groups aided in the solubility of the macrocycle after alkyne metathesis. The dibromo-*cis*-stilbene precursor (**3**) was synthesized via a Wittig reaction between a phosphonium salt (**1**) and an aldehyde (**2**). The crude reaction mixture contained a *cis*-to-*trans* ratio of 5:2. Column chromatography was used to isolate the *cis*-isomer in 60% yield. Pd-catalyzed Kumada coupling with 1-propynylmagnesium bromide resulted in the dipropynyl building block (**4**). Mo(VI)-catalyzed alkyne metathesis provided the tetrameric macrocycle **5** almost exclusively in 90% yield. The crude reaction mixture also contained miniscule amounts of macrocycles ranging from trimeric to nonameric species that were detected by MALDI mass spectrometry (Fig. S11, ESI). Further purification can be performed through recrystallization in 1,2-dichloroethane.

Macrocycle **5** contains four alkenes and four alkynes. The planned CPPA synthesis route required selective bromination on the alkenes over the alkynes. Generally, alkenes undergo bromination faster than alkynes.[36] For instance, Iyoda and coworkers prepared arylene-ethynylene macrocycles by selective bromination of alkenes with Br_2 in the presence of alkynes.[37] However, bromination of macrocycle **5** using Br_2 yielded a complex mixture with partially brominated alkynes. Therefore, tetrabutylammonium tribromide ($TBABr_3$) was chosen as a milder and more selective brominating reagent.[38, 39] Treatment of macrocycle **5** with $TBABr_3$ overnight at room temperature resulted in a clean conversation to the desired octa-brominated macrocycle. Without further purification, the brominated macrocycle was subjected to dehydrobromination using potassium *tert*-butoxide. Removal of the solvent (THF) and filtering through a pad of neutral alumina using toluene resulted in **[8]CPPA-Me$_8$** in 80% yield over two steps. To date, we have been able to scale the reaction enough to synthesize 580 mg of the carbon nanohoop in a single batch. We note that the reaction and work-up were performed in a nitrogen-filled glovebox considering the instability of **[8]CPPA-Me$_8$** in air, which is consistent with observations made by Kawase and Oda on **[8]CPPA**.

Single crystals of **[8]CPPA-Me$_8$** suitable for X-ray crystallographic analysis were obtained by slow diffusion of pentane into a concentrated solution of **[8]CPPA-Me$_8$** in toluene

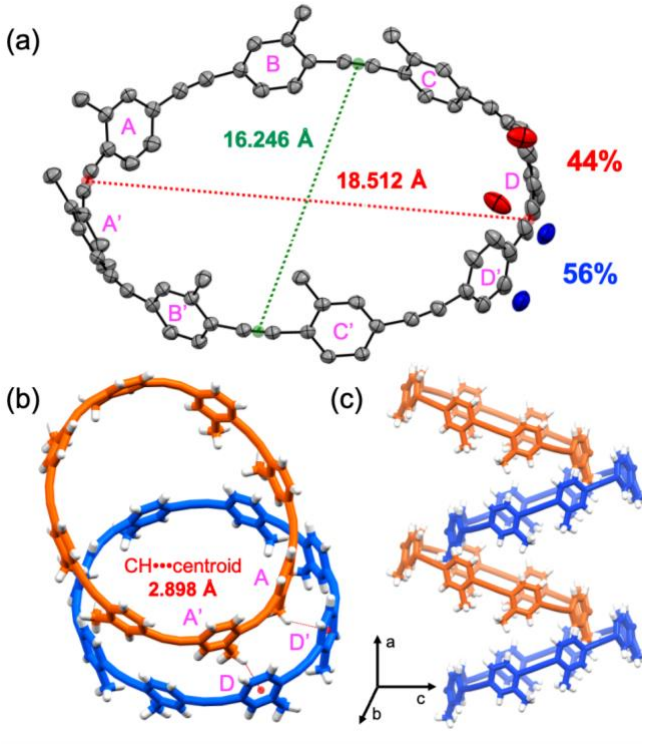


Figure 1. (a) X-ray crystal structure of **[8]CPPA-Me$_8$** with an elliptic shape. Two pairs of disordered methyl groups with populations of 56% (blue, down) and 44% (red, up). (b) Two CH···π interactions between two nanohoops. (c) Zig-zag packing pattern along the a-axis. Disordered methyl groups were omitted for clarity.

(*Pnma* space group). The solid-state **[8]CPPA-Me$_8$** formed an ellipse with a major axis length of 18.512 Å and a minor axis length of 16.246 Å. These values were comparable to those of **[8]CPPA** reported by Kawase and Oda (major: 18.394 Å, minor: 16.261 Å).[40] Six out of eight methyl groups were facing the same "up" direction (Fig. 1a). Two methyl groups close to the major axis were disordered either up or down with a population ratio of 44:56, respectively. The nanohoops exhibited intermolecular C-H···π interactions where one pair of methyl groups on phenylene A and A' are in close contact to phenylene D' and D of another nanohoop, respectively (Fig. 1b). The C-H to phenylene centroid distance was 2.898 Å. Additionally, while six phenylenes (B, B', C, C', D, D') were nearly perpendicular (90 ± 10°) to the plane of the nanohoop, phenylenes A and A' were leaning outwards by 112° (Fig. S13, ESI) to strengthen the C-H···π interaction. The nanohoops were packed in a zig-zag fashion along the a-axis, connected by the aforementioned C-H···π interactions (Fig. 1c).

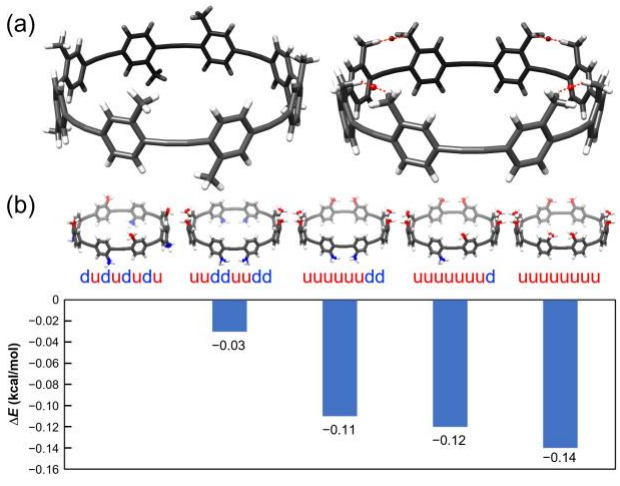


Figure 2. (a) Comparison of the energy-minimized structures of two conformers of **[8]CPPA-Me$_8$** with all alternating methyl groups (left) and all methyl groups positioned on the same rim (right). Attractive non-covalent bonding interactions (dashed lines) were identified by the presence of bond critical points (red spheres) in atoms-in-molecules analysis of the DFT calculations. (b) Relative energies of select conformations of **[8]CPPA-Me$_8$**. The conformation notations are simplified to denote methyl group orientation with up (u, red) and down (d, blue) labels. DFT calculations using the B3LYP functional and the 6-31G+(d,p) basis set.

In order to further understand the conformational states of **[8]CPPA-Me$_8$**, we performed gas-phase DFT calculations on 18 of the 43 possible conformations that are accessible by different "up" (u) or "down" (d) orientations of the methyl groups (see Fig. S14 and S15 in ESI for detailed stereochemical analysis). Unlike the *dududud* conformation with fully alternating methyl groups (Fig. 2a, left), the *uuuuuuuu* conformation with all methyl groups located on the same rim (Fig. 2a, right) exhibits attractive hydrogen-hydrogen bonding[41, 42] interactions between adjacent methyl groups. Overall, the DFT calculations agree with the conformations observed in solid state, where the most stable conformers are those with most (*uuuuuudd*, *uuuuuuud*) or all (*uuuuuuuu*) of the methyl groups being located on the same rim of the macrocycle (Fig. 2b).

In summary, alkyne metathesis was implemented to selectively synthesize a tetrameric macrocycle in high yield. Installation of strained-alkynes via bromination and subsequent dehydrobromination of *cis*-stilbenes provided the desired nanohoop in a scalable manner with high yields. Notably, this synthetic strategy allowed us to circumvent the reductive aromatization which previously limited the scalability of CPPA syntheses. We envision the synthetic method described here can be adapted for the modular synthesis of other CPPA derivatives with various substituents and enable further investigations on the strain-induced reactivity[43-46] of the alkynes.

S. L. thanks the support from the National Science Foundation (NSF CHE 1956302) and start-up funds provided by the College of Science and the Office of Research and Economic Development at Louisiana State University. C. J. B thanks the College of Engineering and Applied Science at the University of Colorado Boulder for startup funds. This work utilized resources from the University of Colorado Boulder Research Computing Group, which is supported by the National Science Foundation (awards ACI-1532235 and ACI-1532236), the University of Colorado Boulder, and Colorado State University.

Conflicts of interest

There are no conflicts to declare.

References

1. R. Jasti, J. Bhattacharjee, J. B. Neaton and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2008, **130**, 17646-17647.
2. H. Takaba, H. Omachi, Y. Yamamoto, J. Bouffard and K. Itami, *Angew. Chem. Int. Ed.*, 2009, **48**, 6112-6116.
3. S. Yamago, Y. Watanabe and T. Iwamoto, *Angew. Chem. Int. Ed.*, 2010, **49**, 757-759, S757/751-S757/756.
4. Y. Luan and H. Cong, *Synlett*, 2017, **28**, 1383-1388.
5. E. R. Darzi and R. Jasti, *Chem. Soc. Rev.*, 2015, **44**, 6401-6410.
6. V. K. Patel, E. Kayahara and S. Yamago, *Chem. Eur. J.*, 2015, **21**, 5742-5749.
7. E. R. Darzi, B. M. White, L. K. Loventhal, L. N. Zakharov and R. Jasti, *J. Am. Chem. Soc.*, 2017, **139**, 3106-3114.
8. T. Kawanishi, K. Ishida, E. Kayahara and S. Yamago, *J. Org. Chem.*, 2020, **85**, 2082-2091.
9. E. Kayahara, L. Sun, H. Onishi, K. Suzuki, T. Fukushima, A. Sawada, H. Kaji and S. Yamago, *J. Am. Chem. Soc.*, 2017, **139**, 18480-18483.
10. E. Kayahara, V. K. Patel, J. Xia, R. Jasti and S. Yamago, *Synlett*, 2015, **26**, 1615-1619.
11. J. Xia, J. W. Bacon and R. Jasti, *Chem. Sci.*, 2012, **3**, 3018-3021.
12. Y. Segawa, M. Kuwayama, Y. Hijikata, M. Fushimi, T. Nishihara, J. Pirillo, J. Shirasaki, N. Kubota and K. Itami, *Science*, 2019, **365**, 272-276.
13. T. Iwamoto, Y. Watanabe, T. Sadahiro, T. Haino and S. Yamago, *Angew. Chem. Int. Ed.*, 2011, **50**, 8342-8344.
14. N. Ozaki, H. Sakamoto, T. Nishihara, T. Fujimori, Y. Hijikata, R. Kimura, S. Irle and K. Itami, *Angew. Chem. Int. Ed.*, 2017, **56**, 11196-11202.

15. B. M. White, Y. Zhao, T. E. Kawashima, B. P. Branchaud, M. D. Pluth and R. Jasti, *ACS Cent. Sci.*, 2018, **4**, 1173-1178.
16. E. J. Leonhardt and R. Jasti, *Nat. Rev. Chem.*, 2019, **3**, 672-686.
17. T. Kawase, H. R. Darabi and M. Oda, *Angew. Chem. Int. Ed.*, 1996, **35**, 2664-2666.
18. T. Kawase, N. Ueda, K. Tanaka, Y. Seirai and M. Oda, *Tetrahedron Lett.*, 2001, **42**, 5509-5511.
19. K. Miki and K. Ohe, *Chem. Eur. J.*, 2020, **26**, 2529-2575.
20. K. Miki, K. Saiki, T. Umeyama, J. Baek, T. Noda, H. Imahori, Y. Sato, K. Suenaga and K. Ohe, *Small*, 2018, **14**, 1800720.
21. N. J. Agard, J. A. Prescher and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2004, **126**, 15046-15047.
22. S. Lee, E. Chenard, D. L. Gray and J. S. Moore, *J. Am. Chem. Soc.*, 2016, **138**, 13814-13817.
23. T. A. Schaub, J. T. Margraf, L. Zakharov, K. Reuter and R. Jasti, *Angew. Chem. Int. Ed.*, 2018, **57**, 16348-16353.
24. K. Miki, T. Matsushita, Y. Inoue, Y. Senda, T. Kowada and K. Ohe, *Chem. Commun.*, 2013, **49**, 9092-9094.
25. M. Chiu, B. H. Tchitchanov, D. Zimmerli, I. A. Sanhueza, F. Schoenebeck, N. Trapp, W. B. Schweizer and F. Diederich, *Angew. Chem. Int. Ed.*, 2015, **54**, 349-354.
26. A. Furstner, *Angew. Chem. Int. Ed.*, 2013, **52**, 2794-2819.
27. H. Ehrhorn and M. Tamm, *Chem. Eur. J.*, 2019, **25**, 3190-3208.
28. J. Heppekausen, R. Stade, R. Goddard and A. Furstner, *J. Am. Chem. Soc.*, 2010, **132**, 11045-11057.
29. W. Zhang and J. S. Moore, *J. Am. Chem. Soc.*, 2005, **127**, 11863-11870.
30. W. Zhang, S. Kraft and J. S. Moore, *Chem. Commun.*, 2003, 832-833.
31. G. R. Kiel, H. M. Bergman and T. D. Tilley, *Chem. Sci.*, 2020, **11**, 3028-3035.
32. X. Zhou, R. R. Thompson, F. R. Fronczek and S. Lee, *Org. Lett.*, 2019, **21**, 4680-4683.
33. D. A. Dadley and A. G. Evans, *J. Chem. Soc. B*, 1968, 107-111.
34. G. Levin, J. Jagur-Grodzinski and M. Szwarc, *Trans. Faraday Soc.*, 1971, **67**, 768-771.
35. G. Levin, J. Jagur-Grodzinski and M. Szwarc, *J. Am. Chem. Soc.*, 1970, **92**, 2268-2275.
36. P. W. Robertson, W. E. Dasent, R. M. Milburn and W. H. Oliver, *J. Chem. Soc.*, 1950, 1628-1630.
37. Y. Jun, O. Masanori, T. Futoshi, N. Tomohiko, K. Yoshiyuki, N. Tohru, Y. Masato and I. Masahiko, *Chemistry Letters*, 2008, **37**, 784-785.
38. M. K. Chaudhuri, A. T. Khan, B. K. Patel, D. Dey, W. Kharmawophlang, T. R. Lakshmiprabha and G. C. Mandal, *Tetrahedron Lett.*, 1998, **39**, 8163-8166.
39. I. Saikia, A. J. Borah and P. Phukan, *Chem. Rev.*, 2016, **116**, 6837-7042.
40. T. Kawase, Y. Seirai, H. R. Darabi, M. Oda, Y. Sarakai and K. Tashiro, *Angew. Chem. Int. Ed.*, 2003, **42**, 1621-1624.
41. C. F. Matta, J. Hernández-Trujillo, T.-H. Tang and R. F. W. Bader, *Chem. Eur. J.*, 2003, **9**, 1940-1951.
42. M.-L. Y. Riu, G. Bistoni and C. C. Cummins, *J. Phys. Chem. A*, 2021, **125**, 6151-6157.
43. E. M. Sletten and C. R. Bertozzi, *Acc. Chem. Res.*, 2011, **44**, 666-676.
44. F. R. Fischer and C. Nuckolls, *Angew. Chem. Int. Ed.*, 2010, **49**, 7257-7260.
45. H. Jeong, S. von Kugelgen, D. Bellone and F. R. Fischer, *J. Am. Chem. Soc.*, 2017, **139**, 15509-15514.
46. S. von Kugelgen, I. Piskun, J. H. Griffin, C. T. Eckdahl, N. N. Jarenwattananon and F. R. Fischer, *J. Am. Chem. Soc.*, 2019, **141**, 11050-11058.