Helical Structures

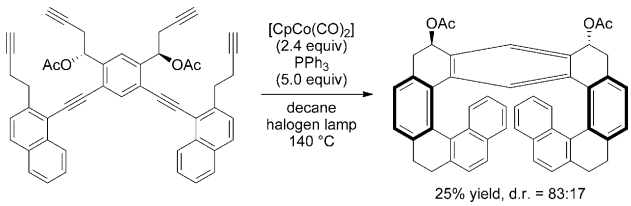
DOI: 10.1002/anie.201404810

Enantioselective Synthesis of [9]- and [11]Helicene-like Molecules: Double Intramolecular [2+2+2] Cycloaddition**

*Yuki Kimura, Naohiro Fukawa, Yuta Miyauchi, Keiichi Noguchi, and Ken Tanaka**

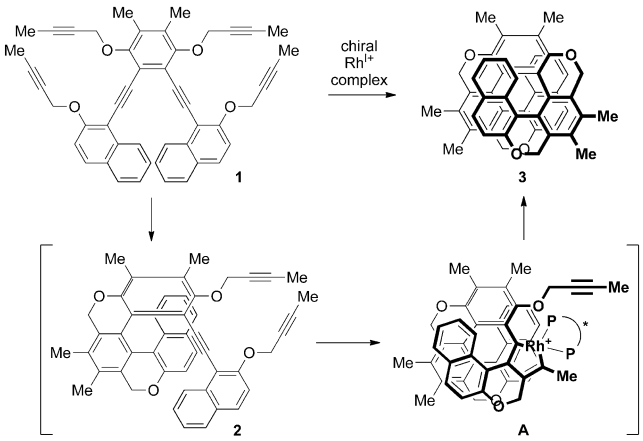
Abstract: *The enantioselective synthesis of completely ortho-fused [9]- and [11]helicene-like molecules has been achieved through a rhodium-mediated, intramolecular, double [2+2+2] cycloaddition of phenol- or 2-naphthol-linked hexaynes. Crystal structures and photophysical properties of these [9]- and [11]helicene-like molecules have also been disclosed.*

Higher-order helicenes and helicene-like molecules possess fascinating, long helical structures,[1] however, their enantioselective synthesis is difficult because of steric hindrance.[2] To date, the enantioselective synthesis of [9]helicenes and helicene-like molecules have been achieved.[3–6] For example, the transition-metal-mediated enantioselective intramolecular [2+2+2] cycloadditions[7] of triynes have been applied to the synthesis of [6]- and [7]helicene-like molecules.[3,4] Stará, Starý, and co-workers pioneered this strategy in the cobalt- or nickel-catalyzed enantioselective intramolecular [2+2+2] cycloaddition, thus leading to [6]helicene-like molecules.[3] Following this pioneering work, our research group accomplished the enantioselective synthesis of sterically more demanding [7]helicene-like molecules using the cationic rhodium(I)/chiral bis(phosphine) complex to catalyze the intramolecular [2+2+2] cycloaddition of 2-naphthol-linked triynes.[4] Subsequently, the enantioselective synthesis of [7]- and [9]helicene-like molecules was achieved using the cationic rhodium(I)/chiral bis(phosphine) complex to catalyze a double intermolecular [2+2+2] cycloaddition between 2-naphthol- or biaryl-linked tetraynes and 1,4-diynes.[5] In 2009, Stará, Starý, and co-workers reported the cobalt-mediated diastereoselective intramolecular double [2+2+2] cycloaddition of a chiral homopropargyl alcohol-derived hexayne, thus leading to a [11]helicene-like molecule (Scheme 1).[8] However, the molecule thus obtained is not the completely *ortho*-fused polycyclic compound and contains three sterically less demanding, *para*-fused central rings.



Scheme 1. Diastereoselective intramolecular double [2+2+2] cycloaddition of hexayne to produce a partially *para*-fused [11]helicene-like molecule. Cp = cyclopentadienyl.

To access a sterically more demanding, completely *ortho*-fused [11]helicene-like molecule[9] starting from commercially available 2-naphthol, we designed an enantioselective rhodium-mediated, double intramolecular [2+2+2] cycloaddition of the 2-naphthol-linked hexayne **1**, thus leading to the [11]helicene-like molecule **3** (Scheme 2). The first cycloaddition of **1** proceeded smoothly to afford the [6]helicene-like molecule **2**. However, the second cycloaddition, leading to **3**, is troublesome because it proceeds through the sterically



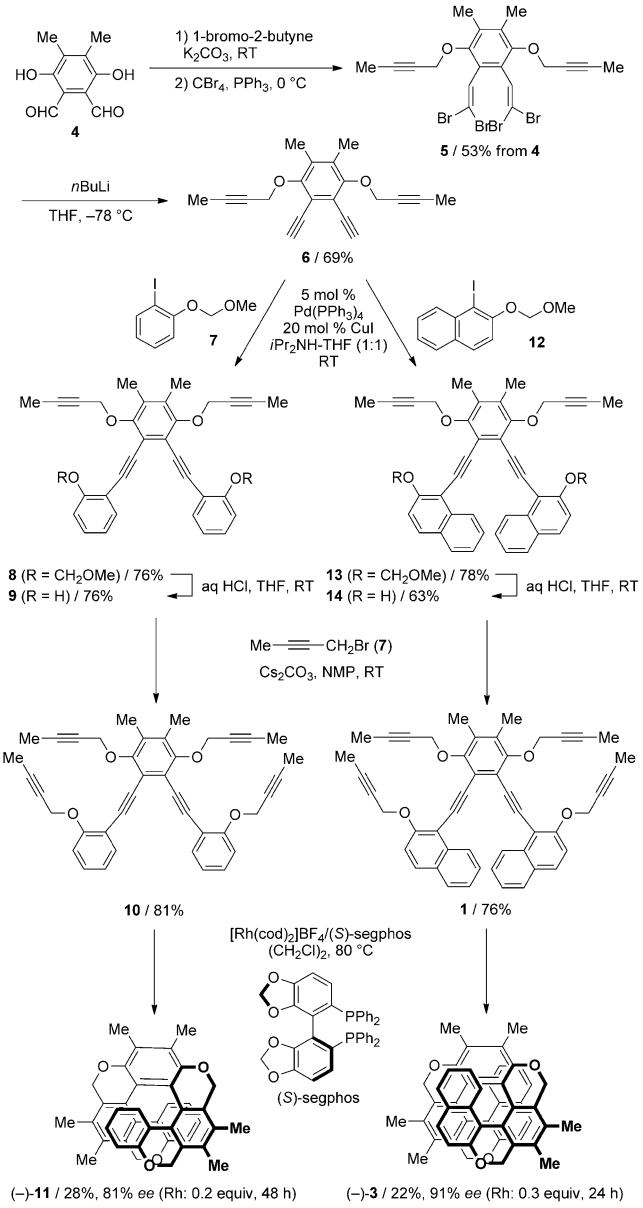
Scheme 2. Enantioselective double intramolecular [2+2+2] cycloaddition of the hexayne **1** to produce the completely *ortho*-fused [11]helicene-like molecule (−)-**3**.

[*] Prof. Dr. K. Tanaka
Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology
Ookayama, Meguro-ku, Tokyo 152-8550 (Japan)
E-mail: ktanaka@apc.titech.ac.jp
Homepage: http://www.tuat.ac.jp/~tanaka-k/
Y. Kimura, N. Fukawa, Y. Miyauchi, Prof. Dr. K. Tanaka
Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology
Koganei, Tokyo 184-8588 (Japan)
Prof. Dr. K. Tanaka
Japan Science and Technology Agency, ACT-C
4-1-8 Honcho, Kawaguchi, Saitama, 332-0012 (Japan)
Prof. Dr. K. Noguchi
Instrumentation Analysis Center, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588 (Japan)

[**] This work was supported partly by ACT-C from Japan Science and Technology Agency (Japan) and a Grant-in-Aid for Scientific Research (No. 20675002) from the Ministry of Education, Culture, Sports, Science and Technology (Japan). We are grateful to Takasago International Corporation for the gift of segphos and Umicore for generous support in supplying the rhodium complex.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404810.

demanding rhodacycle **A**, the bottom of which is covered completely by the naphthalene ring. Herein we disclose the enantioselective synthesis of completely *ortho*-fused [9]- and [11]helicene-like molecules by the rhodium-mediated, double intramolecular [2+2+2] cycloaddition of hexaynes.[10]

To verify the feasibility of the above process, we first examined the enantioselective synthesis of the [9]helicene-like molecule **11** by the intramolecular [2+2+2] cycloaddition of the phenol-linked hexayne **10** using a cationic rhodium(I)/chiral bis(phosphine) complex (Scheme 3). The hexayne **10** was prepared starting from the known phthalaldehyde derivative **4**.[11] Propargylation followed by the Corey–Fuchs reaction of **4** furnished the tetrabromide **5**. Treatment of **5** with *n*-butyllithium furnished the tetrayne **6**. The palladium-catalyzed Sonogashira cross-coupling of **6** with **7** afforded **8**.



Scheme 3. Enantioselective synthesis of [9]- and [11]helicene-like molecules (−)-**11** and (−)-**3**. cod = 1,5-cyclooctadiene, THF = tetrahydrofuran.

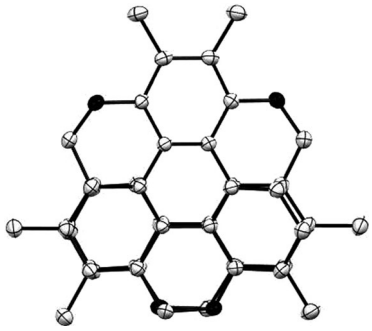


Figure 1. ORTEP diagram of the [9]helicene-like molecule (±)-**11** (top view) with ellipsoids at 30% probability. Hydrogen atoms are omitted for clarity.

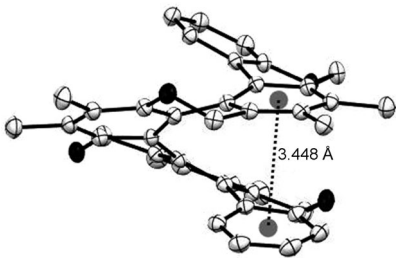


Figure 2. ORTEP diagram of (±)-**11** (side view) with ellipsoids at 30% probability. Hydrogen atoms are omitted for clarity.

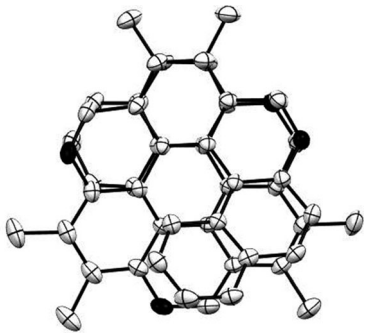


Figure 3. ORTEP diagram of the [11]helicene-like molecule (−)-**3** (top view) with ellipsoids at 30% probability. Hydrogen atoms are omitted for clarity.

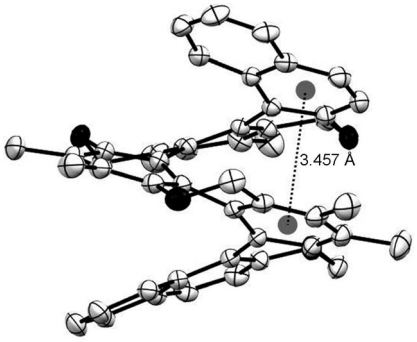


Figure 4. ORTEP diagram of (−)-**3** (side view) with ellipsoids at 30% probability. Hydrogen atoms are omitted for clarity.

Acid hydrolysis of the methoxymethyl (MOM) protecting group furnished the phenol derivative **9**, and propargylation of **9** afforded the hexayne **10**. With the desired **10** in hand, the rhodium-mediated enantioselective intramolecular [2+2+2] cycloaddition of **10** was examined. After screening the reaction conditions, it was found that the desired double cycloaddition proceeded at 80 °C using (*S*)-segphos as a chiral ligand to give the desired [9]helicene-like molecule (−)-**11** with a good *ee* value.

The successful enantioselective synthesis of (−)-**11** prompted our investigation into the enantioselective synthesis of the sterically more demanding **3** (Scheme 3). The Sonogashira cross-coupling of **6** with **12** furnished the tetrayne **13**. Acid hydrolysis of the MOM protecting group furnished naphthol-derivative **14** and propargylation of **14** afforded the hexayne **1**. Pleasingly, the use of the same rhodium complex at 80 °C afforded the desired [11]helicene-like molecule (−)-**3** with a higher *ee* value than that of (−)-**11**, although the product yield was lower than that of (−)-**11**.

The structures of these higher-order helicene-like molecules were unambiguously confirmed by X-ray crystallographic analyses of racemic (±)-**11** and enantiopure (−)-**3** (Figures 1–4).[12] As shown in the top views (Figures 1 and 3), three and five rings are completely overlapped in (±)-**11** and (−)-**3**, respectively. As shown in the side views (Figures 2 and 4), similar distortions were observed for (±)-**11** and (−)-**3**. The distance between two overlapped benzene rings is 3.448 Å for (±)-**11**, and 3.457 Å for (−)-**3**, which are very close to each other.

Photophysical properties of the [9]- and [11]helicene-like molecules are shown in Table 1. The [11]helicene-like molecule (−)-**3** showed a red-shift of the first absorption maxima compared with that of the [9]helicene-like molecule (±)-**11**. In contrast, almost the same emission maxima were observed for (±)-**11** and (−)-**3**. With respect to fluorescence quantum yields in $CHCl_3$ solution, (±)-**11** showed slightly higher yield than (−)-**3**. Optical rotation values of these helicene-like molecules were also measured. Unexpectedly, the optical rotation value, which is calculated as 100% *ee*, of (−)-**3** was not significantly larger than that of (−)-**11**.

Table 1: Photophysical properties of [9]- and [11]helicene-like molecules.[a]

Compound	Absorption λ_{max} [nm][b]	Fluorescence λ_{max} [nm][b,c]	ϕ_F[b,c]	$[\alpha]_D^{25}$[d]
(−)-**11**	271, 370	470 (370)	0.101 (400)	1118
(−)-**3**	300, 352	468 (350)	0.092 (380)	1228

[a] Measured in $CHCl_3$ at 25 °C. [b] 1.3×10^{-5} M. [c] Excitation wavelength [nm] in brackets. [d] Values are calculated as 100% *ee*.

In conclusion, the enantioselective synthesis of completely *ortho*-fused [9]- and [11]helicene-like molecules has been achieved by the rhodium-mediated intramolecular double [2+2+2] cycloadditions of phenol- or 2-naphthol-linked hexaynes. Crystal structures and photophysical properties of these [9]- and [11]helicene-like molecules have also been studied. Future work will focus on the enantioselective synthesis of novel higher-order helicenes and helicene-like molecules by the enantioselective aromatic ring construction.[13]

Received: April 29, 2014
Published online: June 25, 2014

Keywords: alkynes · cycloaddition · enantioselectivity · helical structures · rhodium

[1] For reviews, see: a) Z. Peng, N. Takenaka, *Chem. Rec.* **2013**, *13*, 28; b) Y. Shen, C.-F. Chen, *Chem. Rev.* **2012**, *112*, 1463; c) R. Amemiya, M. Yamaguchi, *Chem. Rec.* **2008**, *8*, 116; d) A. Rajca, M. Miyasaka in *Functional Organic Materials: Syntheses, Strategies, and Applications* (Eds.: T. J. J. Müller, U. H. F. Bunz), Wiley-VCH, Weinheim, **2007**, p. 543; e) C. Nuckolls, R. Shao, W.-G. Jang, N. A. Clark, D. M. Walba, T. J. Katz, *Chem. Mater.* **2002**, *14*, 773; f) T. J. Katz, *Angew. Chem.* **2000**, *112*, 1997; *Angew. Chem. Int. Ed.* **2000**, *39*, 1921.

[2] For reviews, see: a) M. Gingras, G. Félix, R. Peresutti, *Chem. Soc. Rev.* **2013**, *42*, 1007; b) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 968; c) I. G. Stará, I. Starý in *Science of Synthesis*, *Vol. 45b* (Eds.: J. S. Siegel, Y. Tobe), Thieme, Stuttgart, **2010**, p. 885; d) A. Urbano, *Angew. Chem.* **2003**, *115*, 4116; *Angew. Chem. Int. Ed.* **2003**, *42*, 3986; e) C. Schmuck, *Angew. Chem.* **2003**, *115*, 2552; *Angew. Chem. Int. Ed.* **2003**, *42*, 2448. See also refs [1a–d].

[3] a) I. G. Stará, I. Starý, A. Kollárovič, F. Teplý, Š. Vyskočil, D. Šaman, *Tetrahedron Lett.* **1999**, *40*, 1993; b) F. Teplý, I. G. Stará, I. Starý, A. Kollárovič, D. Šaman, Š. Vyskočil, P. Fiedler, *J. Org. Chem.* **2003**, *68*, 5193; c) A. Jančařik, J. Rybáček, K. Cocq, J. V. Chocholoušová, J. Vacek, R. Pohl, L. Bednárová, P. Fiedler, I. Cisařová, I. Stará, I. Starý, *Angew. Chem.* **2013**, *125*, 10154; *Angew. Chem. Int. Ed.* **2013**, *52*, 9970; d) B. Heller, M. Hapke, C. Fischer, A. Andronova, I. Starý, I. Stará, *J. Organomet. Chem.* **2013**, *723*, 98.

[4] K. Tanaka, A. Kamisawa, T. Suda, K. Noguchi, M. Hirano, *J. Am. Chem. Soc.* **2007**, *129*, 12078.

[5] a) K. Tanaka, N. Fukawa, T. Suda, K. Noguchi, *Angew. Chem.* **2009**, *121*, 5578; *Angew. Chem. Int. Ed.* **2009**, *48*, 5470; b) N. Fukawa, T. Osaka, K. Noguchi, K. Tanaka, *Org. Lett.* **2010**, *12*, 1324; c) Y. Sawada, S. Furumi, A. Takai, M. Takeuchi, K. Noguchi, K. Tanaka, *J. Am. Chem. Soc.* **2012**, *134*, 4080. The enantioselective intramolecular [2+2+2] cycloaddition using iridium(I) and nickel(0) complexes has also been reported: d) T. Shibata, T. Uchiyama, Y. Yoshinami, S. Takayasu, K. Tachikawa, K. Endo, *Chem. Commun.* **2012**, *48*, 1311.

[6] For other recent examples of the enantioselective helicene synthesis, see: [5]helicenes: a) J. Caeiro, D. Peña, A. Cobas, D. Pérez, E. Guitián, *Adv. Synth. Catal.* **2006**, *348*, 2466; [5]helicene-like molecules: b) M. C. Carreño, S. García-Cerrada, A. Urbano, *Chem. Eur. J.* **2003**, *9*, 4118; [7]helicenes: c) A. Grandbois, S. K. Collins, *Chem. Eur. J.* **2008**, *14*, 9323; [7]helicene-like molecules: d) M. C. Carreño, M. González-López, A. Urbano, *Chem. Commun.* **2005**, 611; e) A. Rajca, M. Miyasaka, M. Pink, H. Wang, S. Rajca, *J. Am. Chem. Soc.* **2004**, *126*, 15211; thia[11]helicene-like molecules: f) M. Miyasaka, A. Rajca, M. Pink, S. Rajca, *J. Am. Chem. Soc.* **2005**, *127*, 13806.

[7] For selected reviews that focus on the transition-metal-catalyzed enantioselective [2+2+2] cycloaddition of alkynes, see: a) Y. Shibata, K. Tanaka, *Synthesis* **2012**, 323; b) K. Tanaka, *Chem. Asian J.* **2009**, *4*, 508; c) T. Shibata, K. Tsuchikama, *Org. Biomol. Chem.* **2008**, *6*, 1317; d) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085; e) K. Tanaka, *Synlett* **2007**, 1977. See also ref. [2c].

[8] P. Sehnal, I. G. Stará, D. Šaman, M. Tichý, J. Míšek, J. Cvačka, L. Rulíšek, J. Chocholoušová, J. Vacek, G. Goryl, M. Szymonski, I. Císařová, I. Starý, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 13169.
[9] For examples of the nonasymmetric synthesis of ≥ [11]helicenes and helicene-like molecules, see: [11]helicene-like molecules: a) M. B. Groen, H. Schadenberg, H. Wynberg, *J. Org. Chem.* **1971**, *36*, 2797; thia[11]helicene-like molecules: b) P. G. Lehman, H. Wynberg, *Aust. J. Chem.* **1974**, *27*, 315; c) H. Wynberg, M. B. Groen, *J. Am. Chem. Soc.* **1970**, *92*, 6664; [13]helicene: d) R. H. Martin, G. Morren, J. J. Schurter, *Tetrahedron Lett.* **1969**, *10*, 3683; [11]-, [12]-, and [14]helicenes: e) R. H. Martin, M. Baes, *Tetrahedron* **1975**, *31*, 2135; thiahetero[11]-, -[13]-, and [15]helicene-like molecules: f) K. Yamada, S. Ogashiwa, H. Tanaka, H. Nakagawa, H. Kawazura, *Chem. Lett.* **1981**, 343.
[10] For selected recent examples of the nonphotochemical synthesis of helicenes and helicene-like molecules, see: a) L. Pospíšil, L. Bednárová, P. Štěpánek, P. Slavíček, J. Vávra, M. Hromadová, H. Dlouhá, J. Tarábek, F. Teplý, *J. Am. Chem. Soc.* **2014**, DOI: 10.1021/ja500220j; b) K. Yavari, P. Aillard, Y. Zhang, F. Nuter, P. Retailleau, A. Voituriez, A. Marinetti, *Angew. Chem.* **2014**, *126*, 880; *Angew. Chem. Int. Ed.* **2014**, *53*, 861; c) E. Kaneko, Y. Matsumoto, K. Kamikawa, *Chem. Eur. J.* **2013**, *19*, 11837; d) F. Torricelli, J. Bosson, C. Besnard, M. Chekini, T. Bürgi, J. Lacour, *Angew. Chem.* **2013**, *125*, 1840; *Angew. Chem. Int. Ed.* **2013**, *52*, 1796; e) M. R. Crittall, N. W. G. Fairhurst, D. R. Carbery, *Chem. Commun.* **2012**, *48*, 11181; f) T. Hatakeyama, S. Hashimoto, T. Oba, M. Nakamura, *J. Am. Chem. Soc.* **2012**, *134*, 19600; g) K. Goto, R. Yamaguchi, S. Hiroto, H. Ueno, T. Kawai, H. Shinokubo, *Angew. Chem.* **2012**, *124*, 10479; *Angew. Chem. Int. Ed.* **2012**, *51*, 10333; h) K. Nakano, H. Oyama, Y. Nishimura, S. Nakasako, K. Nozaki, *Angew. Chem.* **2012**, *124*, 719; *Angew. Chem. Int. Ed.* **2012**, *51*, 695.
[11] D. W. Cameron, P. M. Scott, L. Todd, *J. Chem. Soc.* **1964**, 42.
[12] CCDC 999677 [(±)-**11**] and 999676 [(−)-**3**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[13] For a review, see: *Transition-Metal-Mediated Aromatic Ring Construction* (Ed.: K. Tanaka), Wiley, Hoboken, **2013**.

