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Enantioselective construction of new chiral cyclic scaffolds using [2 + 2 + 2] cycloaddition*

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Abstract: Two types of enantioselective [2 + 2 + 2] cycloadditions of triynes using chiral rhodium catalysts are disclosed. The intramolecular reaction of *ortho*-aminophenol-tethered triynes provides chiral tripodal compounds. Consecutive inter- and intramolecular reactions of *ortho*-phenylene-tethered triynes provide chiral tetraphenylenes.

Keywords: asymmetric synthesis; cage compounds; chirality; cycloaddition; enantioselectivity; polyaryl compounds; rhodium; tetraphenylenes; triynes.

INTRODUCTION

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes is the most atom-economical and facile protocol for the construction of a benzene ring. Yamazaki is a pioneer in this field and reported the cobalt complex-mediated trimerization of diphenylacetylene [1]. Vollhardt reported a catalytic reaction using cobalt carbonyl complex: this reaction offered a new route for the preparation of substituted benzenes by alkyne trimerization [2]. As for an enantioselective [2 + 2 + 2] cycloaddition of alkynes, Mori reported the chiral nickel complex-catalyzed intermolecular reaction of triynes with acetylene: in this reaction, an asymmetric carbon atom was generated at the benzylic position of the obtained benzene ring by enantiotopic group selection [3]. Starý reported the chiral nickel complex-catalyzed intramolecular reaction of triynes, which induced helical chirality [4]. Even though these were pioneering and fascinating works, enantioselectivity was not sufficiently high. In 2004, three groups including ours independently reported enantioselective [2 + 2 + 2] cycloaddition using chiral cobalt, iridium, and rhodium catalysts, respectively, for the induction of axial chirality [5]. Since then, various types of enantioselective [2 + 2 + 2] cycloaddition have been comprehensively studied by us and other groups [6]. This manuscript discloses two approaches based on the [2 + 2 + 2] cycloaddition of triynes for the construction of new chiral scaffolds.

In the first part of this manuscript, we mention the intramolecular reaction of branched triynes. The intramolecular cycloaddition of branched molecules provides bridged compounds. We recently reported the enantioselective reaction of various 1,1-disubstituted alkene-tethered enynes and diynes, which were used as branched substrates [7]. In the case of the intramolecular reaction of branched triynes with the same three tethers, two regioisomers of 1,3,5- and 1,2,4-isomers (as two enantiomers) can be obtained (Scheme 1). The intramolecular reactions of carbon- and silicon-branched triynes using a Ziegler-type catalyst were already reported, but the yield of the tripodal cage-type cycloadducts was

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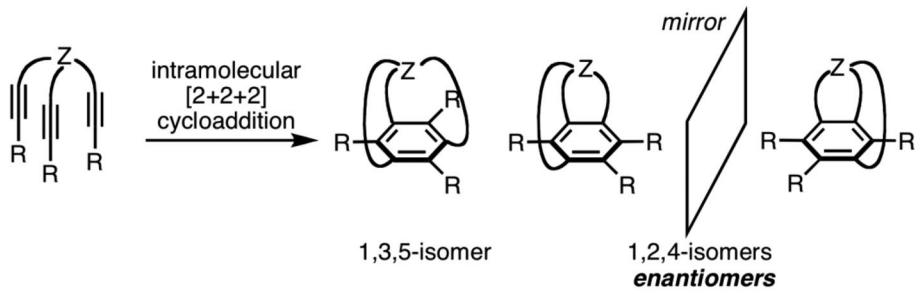
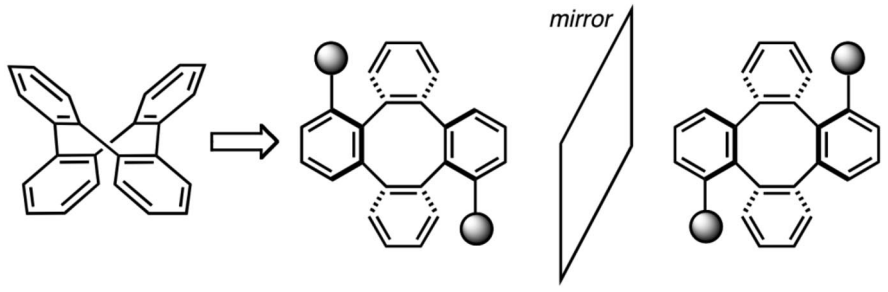


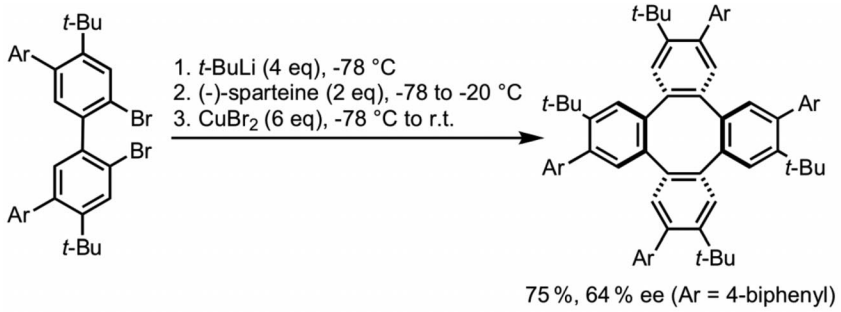
Scheme 1 Intramolecular [2 + 2 + 2] cycloaddition of a general branched triyne.

low to moderate [8]. Thus, we tried to develop the first enantioselective and efficient synthesis of chiral tripodal compounds by intramolecular [2 + 2 + 2] cycloaddition of branched triynes [9,10].

In the second part of this manuscript, we mention the enantioselective preparation of tetraphenylenes by consecutive inter- and intramolecular [2 + 2 + 2] cycloadditions. Tetrabenzo[*a*,*c*,*e*,*g*]cyclooctatetraene, which is referred to as tetraphenylene, is a saddle-shaped molecule, in which the four benzene rings are aligned above and below alternately. Therefore, tetraphenylene is not chiral, but the substitution on the benzene rings can induce the formation of a chiral π-conjugated system because of the high barrier for the flipping of the cyclooctatetraene ring (Scheme 2). There are two major protocols for the synthesis of substituted tetraphenylenes: the Cu-mediated homo-coupling of *ortho*-bimetallated arenes [11] and the [4 + 2] cycloaddition of strained cyclic alkynes with furan along with reductive treatment [12]. Rajca reported an example of enantioselective synthesis, wherein sparteine-based chiral lithium salt was used in Cu-mediated homo coupling, and moderate enantioselectivity was achieved (eq. 1) [13]. Thus, we tried to develop the first highly enantioselective synthesis of chiral tetraphenylenes using a new approach [14].



Scheme 2 The unique structure of tetraphenylene and its chirality.

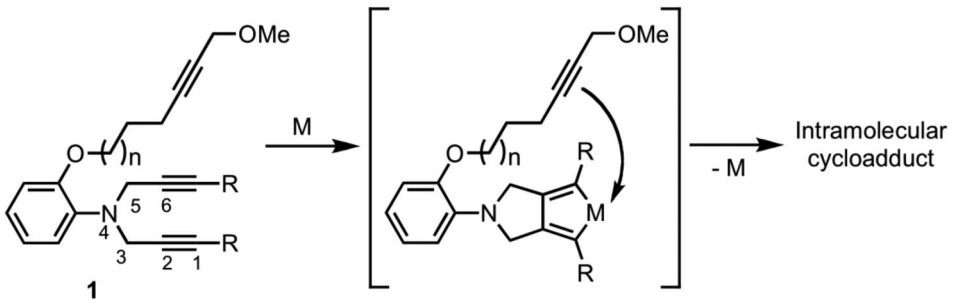


(1)

RESULTS AND DISCUSSION

Intramolecular reaction of *ortho*-aminophenol-tethered triynes for the preparation of chiral tripodal compounds

First, we designed nitrogen-branched triyne **1**, which would realize the selective formation of 1,2,4-isomer by intramolecular reaction (Scheme 3). The reaction is initiated by the oxidative coupling of nitrogen-tethered 1,6-diyne moiety. The resulting metallacyclopentadiene undergoes intramolecular alkyne-insertion prior to the intermolecular one because of its rigid *ortho*-aminophenol structure. Moreover, the coordination of the oxygen of the methoxymethyl group to the metal center facilitates the intramolecular reaction.



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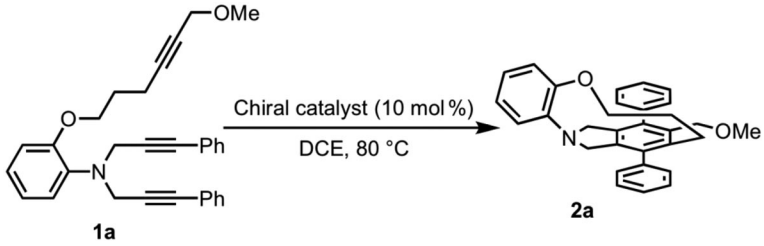
Scheme 3 Advantage of designed nitrogen-branched triyne for the intramolecular reaction.

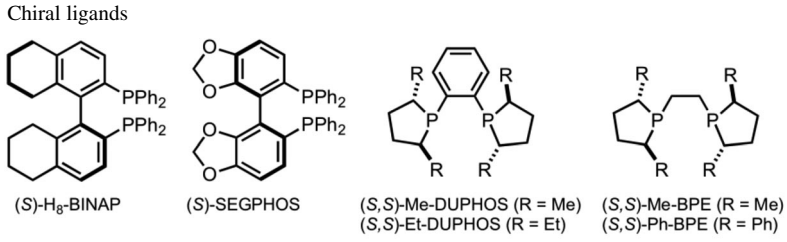
Triyne **1a** was subjected to several reaction conditions (Table 1). When the Rh-BINAP catalyst was used, we obtained the expected tripodal product **2a** in good yield, but the enantiomeric excess was moderate (entry 1). Screening of BINAP derivatives showed that triyne **1a** was completely consumed within 30 min at 80 °C in 1,2-dichloroethane (DCE), and that the yield was good but the enantiomeric excess remained to be moderate (entries 2 and 3). Unlike the conventional Rh-catalyzed enantioselective [2 + 2 + 2] cycloadditions, DUPHOS ligands were preferable for the present cycloaddition, and excellent enantioselectivity was achieved by Me-DUPHOS (entry 4). As the result of further tuning of counter anion (entries 8 and 9), we chose the combination of Me-DUPHOS and triflate as the best one.

Table 1 Screening of the reaction conditions for the Rh-catalyzed cycloaddition.

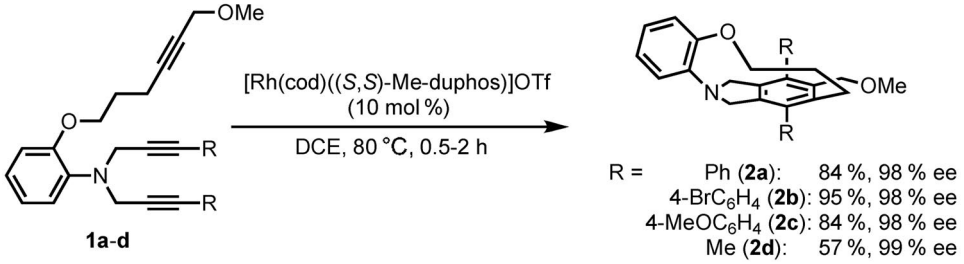


Entry	Chiral catalyst	Time (h)	Yield (%)	Ee (%)
1	$[Rh(cod)_2]BF_4$ + (*S*)-BINAP	0.5	77	40
2	$[Rh(cod)_2]BF_4$ + (*S*)-H_8-BINAP	0.5	81	36
3	$[Rh(cod)_2]BF_4$ + (*S*)-SEGPHOS	0.5	74	56
4	$[Rh(cod)_2]BF_4$ + (*S*,*S*)-Me-DUPHOS	2	70	98
5	$[Rh(cod)_2]BF_4$ + (*S*,*S*)-Et-DUPHOS	2	74	94
6	$[Rh(cod)_2]BF_4$ + (*S*,*S*)-Me-BPE	24	55	46
7	$[Rh(cod)_2]BF_4$ + (*S*,*S*)-Ph-BPE	9	76	91
8	$[Rh(cod)_2]BARF^a$ + (*S*,*S*)-Me-DUPHOS	1	61	94
9	**$[Rh(cod)_2]OTf$ + (*S*,*S*)-Me-DUPHOS**	**1**	**77**	**98**

[a]BARF: tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

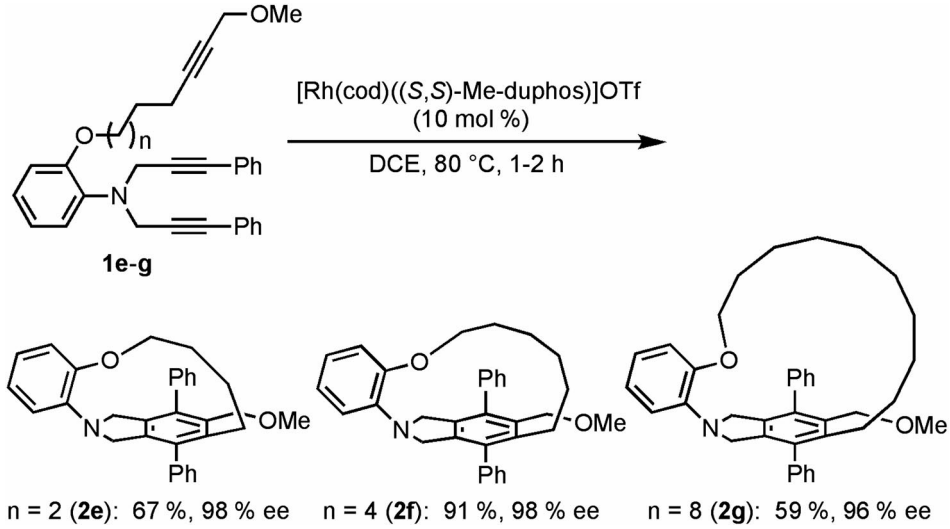


The chiral rhodium complex $[Rh(cod)_2$(*S*,*S*)-Me-duphos]OTf was preliminarily prepared from $[Rh(cod)_2]$OTf and (*S*,*S*)-Me-DUPHOS, and it was used as a catalyst for the reaction of triynes with various substituents on their diyne termini (Scheme 4). Both electron-withdrawing and -donating groups could be introduced as a substituent on the aryl group, and excellent enantiomeric excess of 98 % was achieved. When the methyl group was installed, almost perfect enantioselectivity was achieved, but the yield decreased probably because of the intermolecular side-reactions.



Scheme 4 Cycloaddition of triynes with various substituents on their diyne termini.

We then examined triynes **1e–g** with longer tethers under the same reaction conditions (Scheme 5) and obtained the corresponding products **2e–g** with [9], [11], [15]cyclophane systems, respectively, with excellent enantiomeric excess. These results imply that, even in the [15]cyclophane system, the long carbon ansa chain did not flip to racemize.



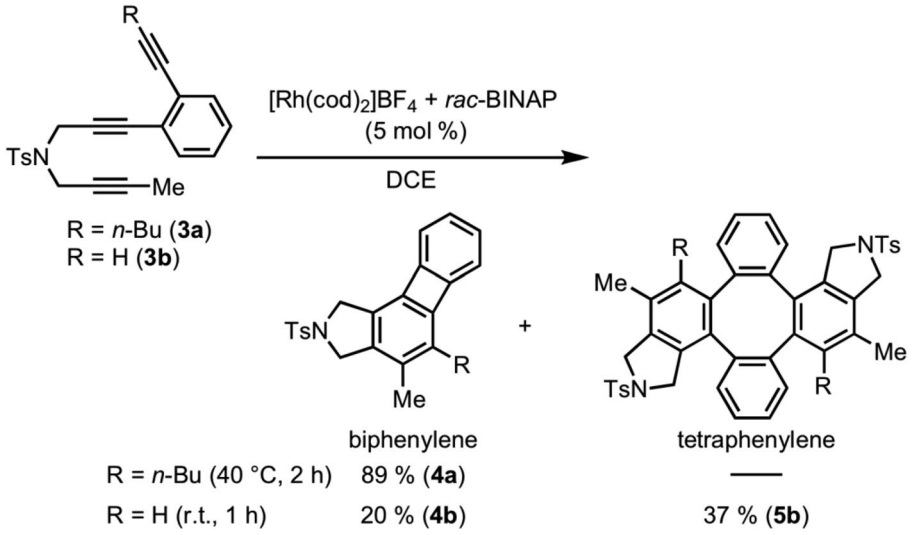
Scheme 5 Cycloaddition of triynes with different tether length.

In order to investigate the origin of the excellent enantioselectivity observed in the present reaction, we investigated the role of oxygen on the alkyne terminus. First, we changed the position of oxygen and reacted triyne **1h** with the but-2-ynyloxy group under the same reaction conditions. We obtained the corresponding cycloadduct **2h**, but the enantiomeric excess of **2h** (88 %) was significantly smaller than that of **2a** (98 %) (eq. 2). We then used triyne **1i** with an oxygen-free alkynyl tether. The reaction proceeds smoothly, and the enantiomeric excess remained unchanged. These results imply that the intramolecular insertion of the alkyne moiety induces as high as ca. 90 % ee, and that the coordination of oxygen to the metal center further improves the enantioselectivity up to 98 %.

(2)

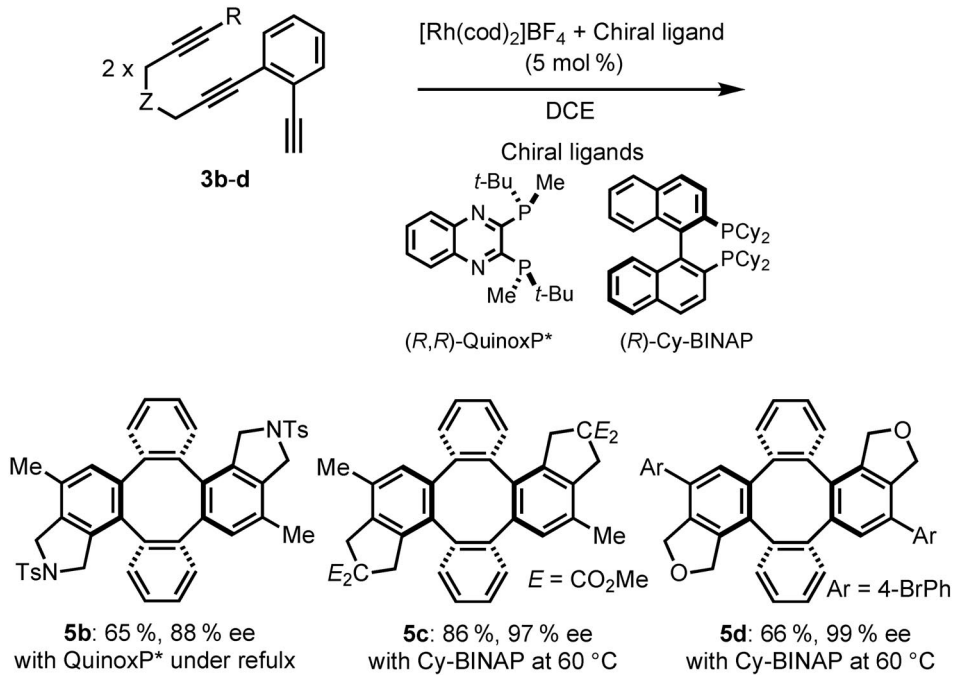
Consecutive inter- and intramolecular reaction of phenylene-bridged triynes for the preparation of chiral tetraphenylenes

When *ortho*-phenylene-tethered triyne **3a** with a butyl group at its terminus (R = *n*-Bu) was reacted in the presence of the Rh-*rac*-BINAP catalyst, an intramolecular reaction proceeded efficiently to give biphenylene **4a** as the only product [15]. In contrast, when unsubstituted triyne **3b** (R = H) was used, biphenylene **4b** was obtained as a minor product and substituted tetraphenylene **5b**, which is a dimer of the triyne, was obtained as the major product (Scheme 6). This is a new protocol for the synthesis of tetraphenylene skeleton. Thus, we tried to develop an enantioselective reaction using a chiral rhodium catalyst.



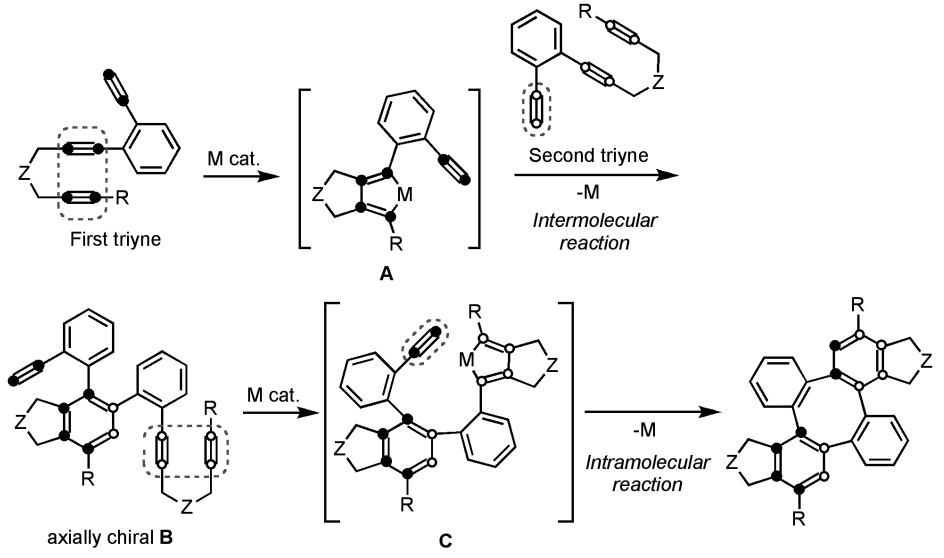
Scheme 6 [2 + 2 + 2] Cycloaddition-based protocol for the preparation of tetraphenylene.

After a thorough investigation of various chiral ligands, the P-chiral ligand, QuinoxP*, which was developed by Imamoto [15], and the electron-rich BINAP derivative, Cy-BINAP (Cy = cyclohexyl), were found to realize high enantioselectivity. Selected examples of the synthesis of chiral tetraphenylenes are listed in Scheme 7.



Scheme 7 Enantioselective synthesis of tetraphenylenes by Rh-catalyzed cycloaddition.

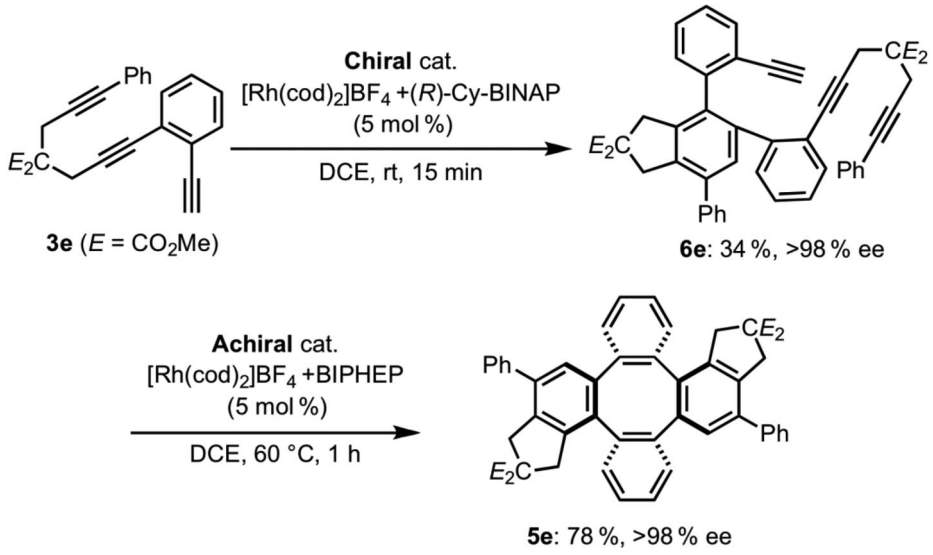
The proposed mechanism for the dimerization of triynes includes consecutive inter- and intramolecular [2 + 2 + 2] cycloadditions (Scheme 8). The oxidative coupling of the 1,6-diyne moiety of the first triyne provides the corresponding metallacyclopentadiene **A**. The intermolecular insertion of the alkyne moiety of the second triyne along with reductive elimination provides the axially chiral cycloadduct **B**. Next, the oxidative coupling of the 1,6-diyne moiety of the second triyne affords the



Scheme 8 Proposed mechanism of consecutive inter- and intramolecular cycloadditions.

metallacycle **C**, and the intramolecular insertion of the remaining alkyne moiety of the first triyne along with reductive elimination provides the substituted tetraphenylene.

In order to verify the above-mentioned scheme, the reaction of carbon-tethered triyne **3e** in the presence of the chiral catalyst at room temperature was investigated; the reaction was quenched within 15 min (Scheme 9). This reaction yielded cycloadduct **6e**, which corresponds to the intermediate **B** in Scheme 8, and its enantiomeric excess was extremely high. Then, the axially chiral compound was subjected to the reaction using achiral Rh-BIPHEP catalyst (BIPHEP: 2,2'-bis(diphenylphosphino)-1,1'-biphenyl). The intramolecular cycloaddition afforded tetraphenylene **5e** without loss of enantiomeric purity.



Scheme 9 Confirmation of proposed mechanism by stepwise process.

CONCLUSION

We realized two types of approaches based on the [2 + 2 + 2] cycloaddition of triynes for the construction of chiral cyclic scaffolds. The intramolecular reaction of *ortho*-aminophenol-tethered nitrogen-branched triynes provided chiral tripodal cage-type compounds. A macrocyclic molecule possessing the [15]cyclophane system could be also constructed. Consecutive inter- and intramolecular reactions of *ortho*-phenylene-tethered triynes afforded chiral-substituted tetraphenylenes as dimerized cycloadducts. In both reactions, Rh-chiral diphosphine catalysts realized excellent enantioselectivity.

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REFERENCES

1. (a) H. Yamazaki, N. Hagihara. *J. Organomet. Chem*. **7**, P22 (1967); (b) Y. Wakatsuki, T. Kuramitsu, H. Yamazaki. *Tetrahedron Lett*. 4549 (1974).
2. (a) W. G. L. Aalbersberg, A. J. Barkovich, R. L. Funk, R. L. Hillard III, K. P. C. Vollhardt. *J. Am. Chem. Soc.* **97**, 5600 (1975); (b) K. P. C. Vollhardt. *Acc. Chem. Res.* **10**, 1 (1977); (c) K. P. C. Vollhardt. *Angew. Chem.* **96**, 525 (1984).
3. Y. Sato, T. Nishimata, M. Mori. *J. Org. Chem.* **59**, 6133 (1994).
4. I. G. Stará, I. Starý, A. Kollárovič, F. Teplý, Š. Vyskočil, D. Šaman. *Tetrahedron Lett.* **40**, 1993 (1999).
5. (a) A. Gutnov, B. Heller, C. Fischer, H.-J. Drexler, A. Spannenberg, B. Sundermann, C. Sundermann. *Angew. Chem., Int. Ed.* **43**, 3795 (2004); (b) T. Shibata, T. Fujimoto, K. Yokota, K. Takagi. *J. Am. Chem. Soc*. **126**, 8382 (2004); (c) K. Tanaka, G. Nishida, A. Wada, K. Noguchi. *Angew. Chem., Int. Ed.* **43**, 6510 (2004).
6. Overview papers by two groups: (a) T. Shibata, K. Tsuchikama. *Org. Biomol. Chem.* 1317 (2008); (b) K. Tanaka. *Chem. Asian. J.* **4**, 508 (2009); see selected papers by other groups: (c) B. Heller, A. Gutnov, C. Fischer, H.-J. Drexler, A. Spannenberg, D. Redkin, C. Sundermann, B. Sundermann. *Chem.—Eur. J.* **13**, 1117 (2007); (d) M. Hapke, K. Kral, C. Fischer, A. Spannenberg, A. Gutnov, D. Redkin, B. Heller. *J. Org. Chem.* **75**, 3993 (2010).
7. (a) T. Shibata, Y. Tahara. *J. Am. Chem. Soc.* **128**, 11766 (2006); (b) T. Shibata, Y. Tahara, K. Tamura, K. Endo. *J. Am. Chem. Soc*. **130**, 3451 (2008).
8. (a) A. J. Hubert, M. Hubert. *Tetrahedron Lett*. **7**, 5779 (1966); (b) R. Damrauer, J. A. Hankin, R. C. Haltiwanger. *Organometallics* **10**, 3962 (1991).
9. Part of this work: T. Shibata, T. Uchiyama, K. Endo. *Org. Lett.* **11**, 3906 (2009).
10. An elegant enantioselective synthesis of dipodal compounds by a Rh-catalyzed intramolecular [2 + 2 + 2] cycloaddition of linear triynes: K. Tanaka, H. Sagae, K. Toyoda, K. Noguchi, M. Hirano. *J. Am. Chem. Soc*. **129**, 1522 (2007).
11. (a) M. Iyoda, S. M. H. Kabir, A. Vorasingha, Y. Kuwatani, M. Yoshida. *Tetrahedron Lett.* **39**, 5393 (1998); (b) S. M. H. Kabir, M. Hasegawa, Y. Kuwatani, M. Yoshida, H. Matsuyama, M. Iyoda. *J. Chem. Soc., Perkin Trans. 1* 159 (2001).
12. (a) H. N. C. Wong, F. Sondheimer. *Tetrahedron* **37**, 99 (1981); (b) Y. D. Xing, N. Z. Huang. *J. Org. Chem.* **47**, 140 (1982).
13. A. Rajca, H. Wang, P. Bolshov, S. Rajca. *Tetrahedron* **57**, 3725 (2001).
14. Part of this work: T. Shibata, T. Chiba, H. Hirashima, Y. Ueno, K. Endo. *Angew. Chem., Int. Ed.* **48**, 8066 (2009).
15. (a) B. C. Berris, Y. H. Lai, K. P. C. Vollhardt. *J. Chem. Soc., Chem. Commun.* **16**, 953 (1982); (b) K. P. C. Vollhardt. *Pure Appl. Chem.* **65**, 153 (1993).
16. (a) T. Imamoto, K. Sugita, K. Yoshida. *J. Am. Chem. Soc.* **127**, 11934 (2005); (b) T. Imamoto, A. Koide. In *Catalysts for the Fine Chemical Synthesis*, Vol. 5, S. Roberts, J. Whittall (Eds.), p. 65, Wiley-VCH, Weinheim (2007).

