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Enantioselective Synthesis of Chiral Tripodal Cage Compounds by [2 + 2 + 2] Cycloaddition of Branched Triynes

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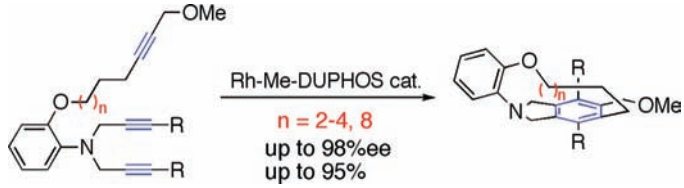
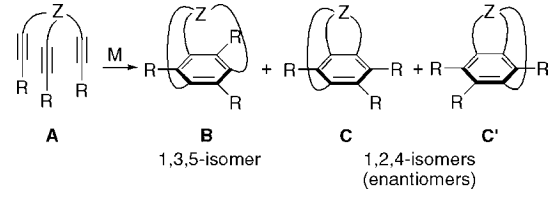
ABSTRACT



Cyclotrimerization of triynes branched by a nitrogen atom of 2-aminophenol yielded planar-chiral tripodal cage compounds. When a cationic Rh−Me-DUPHOS catalyst was used, the cycloadducts were obtained in high yield and excellent ee, and a macrocyclic compound with a [15]cyclophane system was also obtained. This method can be further applied to the synthesis of a triarmed pyridinophane by the intramolecular reaction of a diyne−nitrile.

The transition-metal-catalyzed enantioselective [2 + 2 + 2] cycloaddition of alkynes and alkenes as C2 sources is the most atom-economical and reliable method for the construction of chiral ring systems.[1] Intramolecular reactions, in particular, are fascinating because they provide multicyclic compounds in one pot. In a previous study, we developed an Ir-catalyzed reaction of triynes for the generation of axial chiralities.[2] Then, we and Tanaka's group independently carried out a Rh-catalyzed reaction of enediynes[3] and dienynes[4] for the generation of two central chiralities. In these studies, the substrates were linear compounds, where three C2-unsaturated motifs are present in a straight chain. In contrast, we have recently focused on the reaction of branched compounds because this reaction provides cage compounds with chiralities: a reaction of branched dienynes, wherein the alkyne and alkene moieties are connected by 1,1-disubstituted alkene, give various unique and strained chiral carbon skeletons with multicyclic systems.[5]

Scheme 1. Intramolecular [2 + 2 + 2] Cycloaddition of a Branched Triyne



We next came up with an intramolecular cycloaddition of branched triynes; the [2 + 2 + 2] cycloaddition of triyne **A** yields tripodal compounds, namely 1,3,5-trisubstituted ben-

(1) (a) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, 1317. (b) Tanaka, K. *Chem. Asian J.* **2009**, *4*, 508.

(2) (a) Shibata, T.; Tsuchikama, K.; Otsuka, M. *Tetrahedron: Asymmetry* **2006**, *17*, 614. (b) Shibata, T.; Yoshida, S.; Arai, Y.; Otsuka, M.; Endo, K. *Tetrahedron* **2008**, *64*, 821.

(3) (a) Shibata, T.; Kurokawa, H.; Kanda, K. *J. Org. Chem.* **2007**, *72*, 6521. (b) Tanaka, K.; Nishida, G.; Sagae, H.; Hirano, M. *Synlett* **2007**, 1426.

(4) Sagae, H.; Noguchi, K.; Hirano, M.; Tanaka, K. *Chem. Commun.* **2008**, 3804.

(5) (a) Shibata, T.; Tahara, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11766. (b) Shibata, T.; Tahara, Y.; Tamura, K.; Endo, K. *J. Am. Chem. Soc.* **2008**, *130*, 3451.

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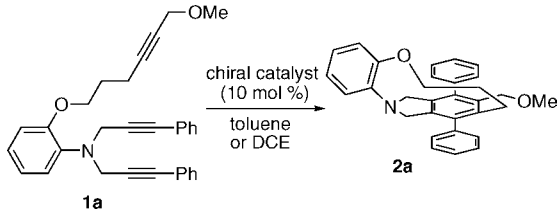
Table 1. Optimization of the Reaction Conditions



entry[a]	chiral catalyst[b]	T/°C	time/h	yield/%	ee/%
1	$[IrCl(cod)]_2$ + 2Me-DUPHOS	60	16	6	86
2	$[IrCl(cod)]_2$ + 2Me-DUPHOS	120	0.3	62	88
3	$[Rh(cod)_2]BF_4$ + Me-DUPHOS	80	2	70	98
4	$[Rh(cod)_2]BF_4$ + Ph-BPE	80	9	76	91
5	$[Rh(cod)_2]BF_4$ + BINAP	80	0.5	77	40
6	$[Rh(cod)_2]BF_4$ + H_8-BINAP	80	0.5	81	36
7	$[Rh(cod)_2]BF_4$ + SEGPHOS	80	0.5	74	56
8	$[Rh(cod)_2]$BARF + Me-DUPHOS	80	1	61	94
9	**$[Rh(cod)_2]$OTf + Me-DUPHOS**	80	1	**77**	**98**

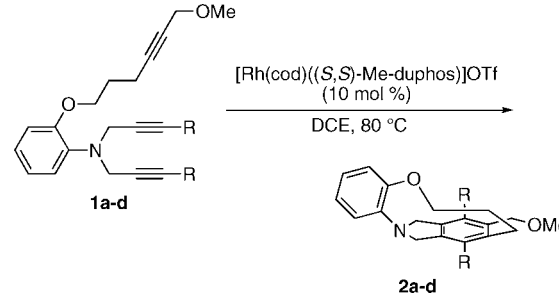
[a] The reaction was examined in toluene (entries 1 and 2) or in DCE (entries 3−9). Triyne **1a** was added dropwise over 10 min to a solution of chiral catalyst except entry 1. [b] (*S*)- or (*S*,*S*)-isomers were used as chiral ligands. Me-DUPHOS: 1,2-bis(2,5-dimethylphospholano)benzene. Ph-BPE: 1,2-bis(2,5-diphenylphospholano)ethane. SEGPHOS: 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. BARF: tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

zene isomer **B** and 1,2,4-trisubstituted benzene isomers **C** and **C′**, which are enantiomers (Scheme 1).[6] To the best of our knowledge, there have been only two reported examples of [2 + 2 + 2] cycloaddition of branched triyne: the reaction of carbon-branched (Z = CH)[7] and silicon-branched (Z = SiBu^t) triynes[8] with the Ziegler catalyst yielded type **B** cycloadduct as a major product, but in low yield. We report herein the first example of enantioselective [2 + 2 + 2] cycloaddition of branched triynes, which yields chiral tripodal cage compounds.[9]

As a model substrate we chose nitrogen-branched triyne **1a** because it has the following three advantages: (1) selective oxidative coupling of dipropargylamine, namely the 1,6-diyne moiety in the triyne, with a metal catalyst, (2) favorable orientation of side chain with alkyne moiety by rigid 2-aminophenol tether, and (3) activation of alkyne moiety by methoxy methyl group.[10] First, we used Ir−Me-DUPHOS (1,2-bis(2,5-dimethylphospholano)benzene) catalyst in toluene, which efficiently operated in the intramolecular reaction of linear triynes.[2a] The reaction proceeded at 60 °C, and the desired cycloadduct **2a** was obtained with high ee (86%); however, the yield was low, probably because of the intermolecular reaction (entry 1 in Table 1).[11] To promote the intramolecular reaction, triyne **1a** was added dropwise over 10 min to a solution of the chiral catalyst at a higher temperature (120 °C), the yield improved drastically (entry 2). Next, we replaced the neutral Ir complex with the cationic Rh complex; the reaction proceeded to completion within 2 h in 1,2-dichloroethane (DCE) at 80 °C, and the enantioselectivity reached 98% using Me-DUPHOS (entry 3).[12] Ph-BPE (1,2-bis(2,5-diphenylphospholano)ethane) gave a better yield, but the enantioselectivity decreased (entry 4). In the present [2 + 2 + 2] cycloaddition, BINAP derivatives were not preferred chiral ligands as only moderate enantioselectivity was achieved with their use (entries 5−7).[13] Finally, we screened the counteranions of the Rh catalyst: triflate gave the best results with regard to both yield and ee (entries 3, 8, and 9).[14]

When isolated Rh−Me-DUPHOS complex was used, the yield improved further and exceeded 80% (entry 1 in Table 2). Under the optimal reaction conditions, triynes **1b**−**d** with other substituents at their diyne termini were examined: the reaction of bromophenyl-substituted triyne **1b** concluded within 30 min, and both the yield and the enantioselectivity were excellent. The electron-donating group on the phenyl group was also acceptable, and the results were the same as those of triyne **1a** (entry 3). In the case of the methyl-substituted triyne **1d**, the corresponding cycloadduct **2d** was

Table 2. Reaction of Triynes Possessing Various Substituents on Their Diyne Termini



entry	R	triyne	time/h	yield/%	ee/%
1	C_6H_5	**1a**	2	84 (**2a**)	98
2	4-BrC_6H_4	**1b**	0.5	95 (**2b**)	98
3	4-(MeO)C_6H_4	**1c**	1	84 (**2c**)	98
4	Me	**1d**	1	57 (**2d**)	99

(6) The synthesis of dipodal compounds, namely *o*, *m*, *p*-cyclophanes by transition-metal-catalyzed [2 + 2 + 2] cycloaddition, is an established protocol: Co catalysts: (a) Moretto, A. F.; Zhang, H.-C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2001**, *123*, 3157. (b) Boñaga, L. V. R.; Zhang, H.-C.; Moretto, A. F.; Ye, H.; Gautheir, D. A.; Li, J.; Leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2005**, *127*, 3473. Rh catalysts: (c) Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 7784. (d) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem.—Eur. J.* **2005**, *11*, 1145.

(7) Hubert, A.; Hubert, M. *Tetrahedron Lett.* **1966**, *46*, 5779.

(8) Damrauer, R.; Hankin, J. A.; Haltiwanger, R. C. *Organometallics* **1991**, *10*, 3962.

(9) Tanaka's group reported an intramolecular reaction of linear triynes. Rh−H_8-BINAP catalyst induced excellent enantioselectivity to give chiral [7]−[10]metacyclophanes but in low yield (10−33%): Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 1522.

(10) The methoxymethyl group efficiently activates the alkyne moiety as a coupling partner of a diyne: (a) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382. (b) Shibata, T.; Arai, Y.; Takami, K.; Tsuchikama, K.; Fujimoto, T.; Takebayashi, S.; Takagi, K. *Adv. Synth. Catal.* **2006**, *348*, 2475.

(11) The formation of highly polar products was ascertained but they could not be identified.

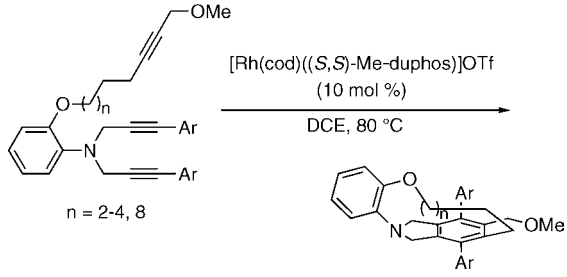
(12) When Ir−Me-DUPHOS catalyst was used in DCE at 80 °C for 2 h, only a trace amount of product **2a** was obtained.

(13) Cationic Rh−BINAP derivatives operated as efficient catalysts in various enatnioselective [2 + 2 + 2] cycloadditions of alkynes; see: Tanaka, K. *Synlett* **2007**, 1977.

obtained in moderate yield and the highest ee of 99% was achieved (entry 4). In triynes **1a**−**d**, there exists a three-carbon tether between phenol and the alkyne moiety, and tripodal cage compounds with the [8]cyclophane skeleton were obtained.

Next, we screened various triynes with longer tethers (Table 3): the reaction of triynes **3** and **5** with C4 and C5

Table 3. Reaction of Triynes with Various Tethers of the Length



entry	*n*	Ar	triyne	time/h	yield/%	ee/%
1	2	Ph	**3**	1	67 (**4**)	98
2	3	Ph	**5**	2	88 (**6**)	98
3	3	4-BrC_6H_4	**7**	1.5	80 (**8**)	97
4	4	Ph	**9**	1	91 (**10**)	98
5	8	Ph	**11**	2	59 (**12**)	96

tethers, respectively, also proceeded smoothly, and the corresponding tripodal cage compounds **4** and **6** were obtained in excellent ee (entries 1 and 2). Recrystallization

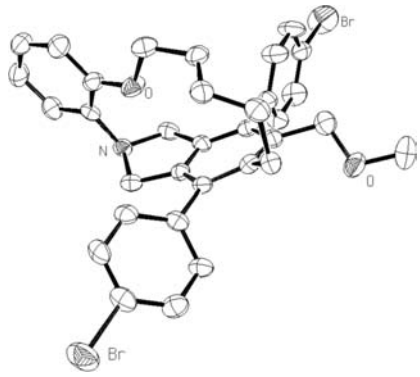
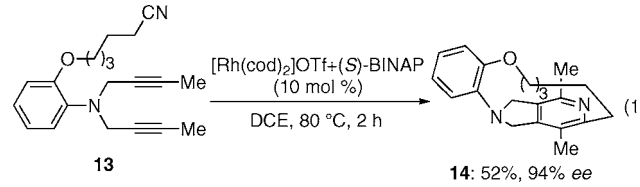


Figure 1. ORTEP diagram of tripodal cycloadduct **8**.

of cycloadduct **8**, derived from bromophenyl-substituted triyne **7**, yielded a single crystal (entry 3), and its structure was determined by X-ray diffraction analysis (Figure 1).[15] When triyne **9** was used in the reaction, the best yield of 91% was achieved along with an excellent ee (entry 4). It is noteworthy that the reaction of triyne **11**, which possesses a C10 tether, also proceeded under the same conditions to afford the planar-chiral cycloadduct **12** in acceptable yield with excellent ee; this implies that the [15]cyclophane structure was definitely constructed, and that the long carbon ansa chain was not flipped to racemize (entry 5).

We further examined a hetero-[2 + 2 + 2] cycloaddition of diyne−nitrile **13** (eq 1).[16] Rh−Me-DUPHOS catalyst did not yield pyridinophane **14**; Rh−BINAP, however, was an efficient catalyst, and planar-chiral cycloadduct **14**[17] was obtained in high ee.[18,19]



In summary, we developed a highly enantioselective intramolecular reaction of nitrogen-branched triynes. A cationic Rh−Me-DUPHOS complex efficiently catalyzed the reaction to yield tripodal cage compounds with tethers having different lengths. The design and synthesis of such functional cage molecules with chiral recognition ability are currently in progress.

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Supporting Information Available: Experimental procedures and spectral data for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Rh−(*R*,*R*)-Me-DUPHOS catalyst surely afforded an opposite enantiomer with the same ee of 98% ee.

(15) The absolute configuration of other cycloadducts was speculated on the basis of that of cycloadduct **8**.

(16) Non-asymmetric intermolecular reactions of diynes with nitrile compounds for the synthesis of pyridinophanes were reported in ref 6a,b.

(17) The absolute configuration of pyridinophane **14** was not determined yet.

(18) The first enantioselective hetero-[2 + 2 + 2] cycloaddition of two alkynes and a nitrile compound, which induced an axial chirality: Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795.

(19) Asymmetric synthesis and use of planar-chiral pyridinophanes: (a) Kanomata, N.; Nakata, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1207. (b) Kanomata, N.; Nakata, T. *J. Am. Chem. Soc.* **2000**, *122*, 4563.