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Enantioselective Synthesis of Planar-Chiral Metacyclophanes through Rhodium-Catalyzed Alkyne Cyclotrimerization

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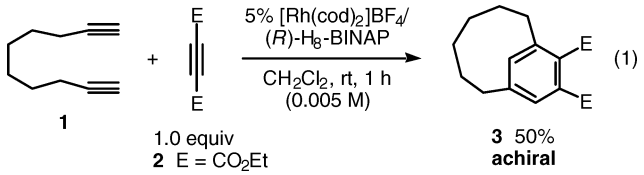
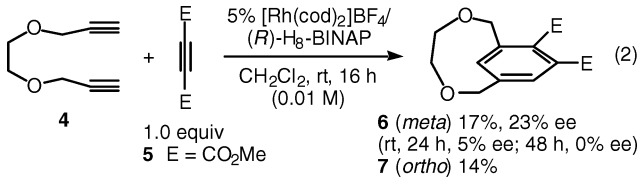
It is well-known that certain cyclophanes having short ansa chains exhibit planar-chirality due to the restricted rotation of the aromatic ring.[1] Despite the potential utility of the planar-chiral cyclophanes in the area of asymmetric synthesis, host−guest chemistry, and material science, the existing methods for the synthesis of them are based on the optical resolution of racemic compounds, and the straightforward enantioselective synthesis has not been reported to date.[2,3] Our recent investigation into $Rh(I)^+/H_8$-BINAP-catalyzed alkyne cyclotrimerization revealed that paracyclophanes can be obtained in good yield from terminal α,ω-diynes and dimethyl acetylenedicarboxylate.[4−6] In this Communication, we describe the first enantioselective synthesis of planar-chiral metacyclophanes through $Rh(I)^+/(R)$-H_8-BINAP-catalyzed alkyne cyclotrimerization.[7]

We recently reported the one-step synthesis of [6]carbametacyclophane **3** from 1,9-decadiyne (**1**) and diethyl acetylenedicarboxylate (**2**) (eq 1).[4] At room temperature, if the hexamethylene chain of **3** resides at one side of the aromatic ring (no ring flip to the other side), **3** can exhibit the planar-chirality.[8] However, the broad signals of the benzylic protons of **3** were observed by ^{1}H NMR analysis, which suggests the ring flip at room temperature.



(1)

Thus, the reaction of ether-linked terminal 1,9-diyne **4** and dimethyl acetylenedicarboxylate (**5**) was investigated to increase the steric strain of the ansa chain. Although the reaction gave desired [6]ether metacyclophane **6** with 23% ee, complete racemization of **6** proceeded at room temperature for 48 h (eq 2).



(2)

Consequently, we have designed the intramolecular cyclotrimerization of triynes bearing substituents at two alkyne termini, which could furnish the corresponding ortho- or metacyclophanes. These metacyclophanes would possess stable planar-chirality because of no ring flip (Scheme 1).[9] Shinokubo, Oshima, and coworker realized this type of macrocyclization using reactive triynes bearing hydrogens at two alkyne termini in an aqueous−organic biphasic system, which diminished the formation of undesired intermolecular reaction products.[5e] However, only [9] and [10]-metacyclophanes were obtained as minor products along with the major orthocyclophanes, and [7] and [8]metacyclophanes possessing short ansa chains were not obtained.[5e,10] Furthermore, the intramolecular cyclotrimerization of less reactive triynes bearing substituents at two alkyne termini have not been realized to date.

Scheme 1

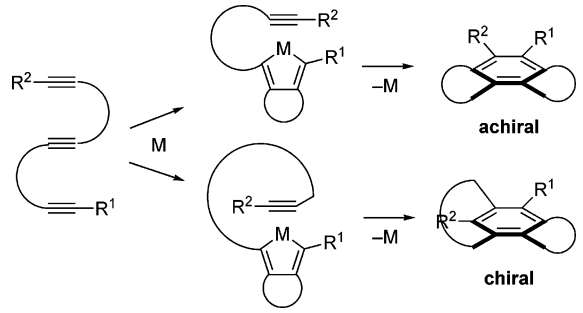
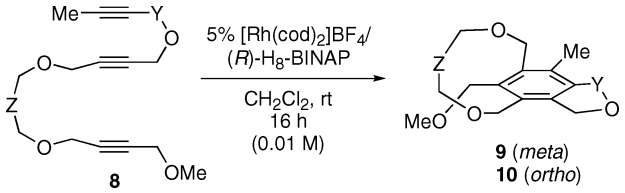


Table 1. Enantioselective Synthesis of Planar-Chiral [7]−[10]Metacyclophanes



entry	8	Y	Z	yield (%)[a] 9 (10)	ee (%) 9
1	**8a**	C=O	CH_2	10 (31)	>98
2	**8b**	C=O	CH_2CH_2	13 (15)	>98
3	**8c**	C=O	$CH_2CH_2CH_2$	10 (40)	98
4	**8d**	C=O	CH_2OCH_2	29[b] (29)	>98
5	**8e**	C=O	$CH_2CH_2CH_2CH_2$	13 (23)	91
6	**8f**	CH_2	CH_2	25 (37)	90
7	**8g**	CH_2	CH_2CH_2	33 (35)	93
8	**8h**	CH_2	$CH_2CH_2CH_2$	21 (15)	94
9[d]	**8i**	CH_2	CH_2OCH_2	30[c] (55)	88
10[d]	**8j**	CH_2	$CH_2CH_2CH_2CH_2$	30 (23)	93

[a] Isolated yield of a pure regioisomer. [b] The corresponding chiral diol of **9d** was isolated in pure form by treatment with $LiAlH_4$. [c] Isolated as a mixture of **9i** and **10i**. [d] Reaction time: 40 h.

We first examined the reaction of methyl- and methoxymethyl-substituted triyne **8a**, bearing an ester-linked 1,6-diyne moiety, using 5% $Rh(I)^+/(R)$-H_8-BINAP at room temperature, which furnished the desired [7]metacyclophane **9a** with excellent enantioselectivity (>98% ee), although **9a** was obtained as a minor isomer (Table 1, entry 1).[11] Fortunately, the reaction of triyne **8f**, bearing an ether-linked 1,6-diyne moiety, furnished the desired [7]metacyclophane **9f** in improved yield with high enantiomeric excess (90% ee, entry 6). Thus, the reactions of a series of triynes **8b**−**e** and **8g**−**j** using

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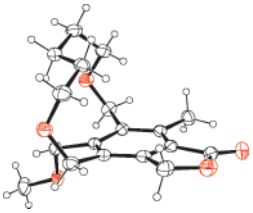
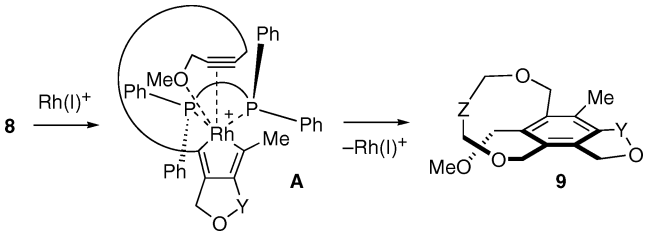


Figure 1. ORTEP diagram of (*R*)-(−)-**9c**.

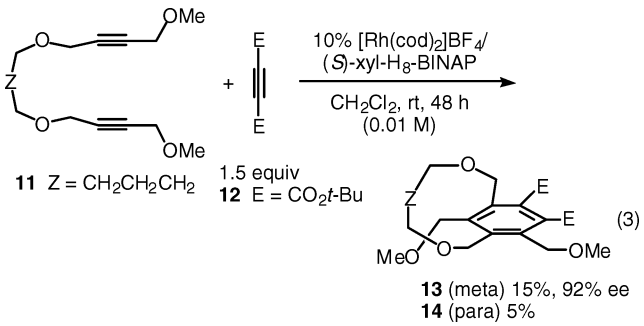
Scheme 2



5% $Rh(I)^+$/(*R*)-H_8-BINAP at room temperature were investigated, which revealed that the corresponding [8]−[10]metacyclophanes **9b**−**e** and **9g**−**j** were obtained in 10−33% yields with high enantiomeric excesses (88 → 98% ee, entries 2−5 and entries 7−10).[12] In general, triynes bearing an ether-linked 1,6-diyne moiety furnished metacyclophanes in higher yield than those bearing an ester-linked 1,6-diyne moiety, but enantioselectivities of the former were lower than those of the latter (entries 6−10 vs entries 1−5). The absolute configuration of [9]metacyclophane (−)-**9c** was determined to be *R* by X-ray crystallographic analysis (Figure 1).

Enantioselectivity would be determined by preferential formation of intermediate **A**, due to the high reactivity of the 1,6-diyne moiety to the rhodium(I) complex, coordination of the terminal methoxy group to the cationic rhodium, and the steric interaction between the ansa chain of **8** and PPh_2 groups of (*R*)-H_8-BINAP (Scheme 2).

The intermolecular variant of this reaction was also investigated (eq 3). The reaction of methoxymethyl-substituted internal diyne **11** with di-*tert*-butyl acetylenedicarboxylate (**12**) using 10% Rh-$(I)^+$/(*S*)-xyl-H_8-BINAP at room temperature furnished the desired [9]metacyclophane **13** in 15% yield with 92% ee as a major isomer (eq 3).



In conclusion, we have achieved the first catalytic enantioselective synthesis of planar-chiral metacyclophanes by means of the cationic rhodium(I)/(*R*)-H_8-BINAP complex-catalyzed alkyne cyclotrimerization. This method represents a versatile new method for the synthesis of planar-chiral [7]−[10]metacyclophanes.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic files (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Results with other BINAP-type ligands: BINAP (9% yield, 91% ee), xyl-BINAP (15% yield, 83% ee), Segphos (7% yield, 26% ee).

(12) The reaction of **8h** by using high catalyst loading (10 mol % of Rh) did not improve the yields of cyclophanes significantly (**9h**: 24% yield, **10h**: 17% yield).

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