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Preparation of functionalized metacyclophanes by intramolecular benzannulation of bisenynes

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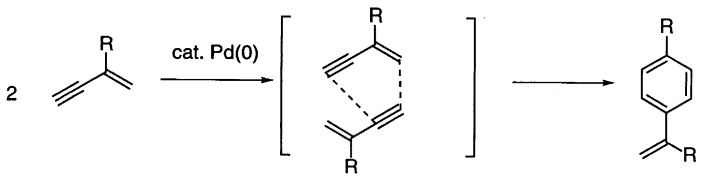
Abstract

We have synthesized a series of novel metacyclophanes by the intramolecular benzannulation of bisenynes in the presence of tetrakis(triphenylphosphine)palladium(0). The usefulness of this synthetic method was demonstrated by the preparation of polyoxometacyclophanes, which we prepared from oligoethylene glycols.

Keywords: enynes; palladium; benzannulation; metacyclophane.

Macrocyclic compounds such as cyclophanes, crown ethers, calixarenes and metallacycles are of interest to organic chemists and the interesting properties of these compounds have been investigated in depth.[1] In the course of our study of transition metal-catalyzed reactions of enynes, we found that 2-substituted conjugated enynes cyclodimerize in the presence of Pd(0) catalysts to give 1,4-disubstituted benzenes in a highly regioselective manner (Eq. (1)).[2a] 4-Substituted conjugated enynes also cyclodimerize to give 1,2,3-trisubstituted benzenes (Eq. (2)).[2b] We applied this benzannulation reaction to the preparation of exomethylene paracyclophanes.[3] Recently, the scope of this benzannulation reaction was expanded, and we succeeded in the synthesis of 1,3-disubstituted benzenes in high yields from the *homo*-benzannulation of 1-substituted enynes bearing electron withdrawing groups such as a carboxyl group (Eq. (3)).[4] This finding led us to consider the synthesis of metacyclophanes by the intramolecular reaction of 1-substituted enynes. In this paper we report the short synthesis of metacyclophanes by the intramolecular cyclization of bisenynes (Eq. (4)).



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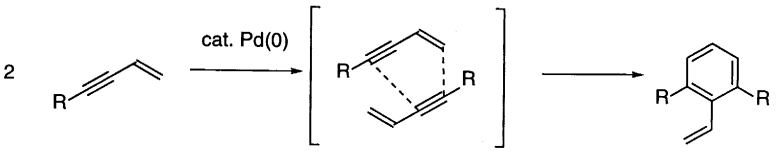

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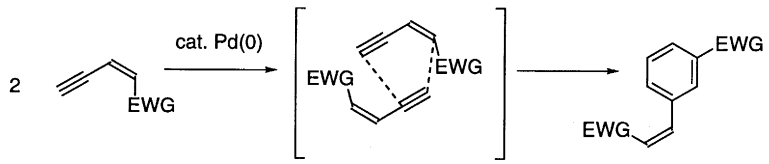

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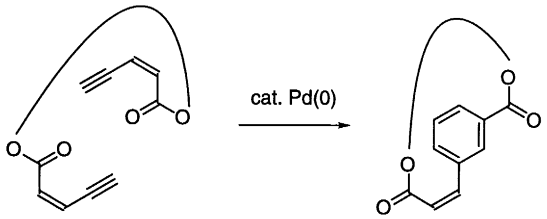
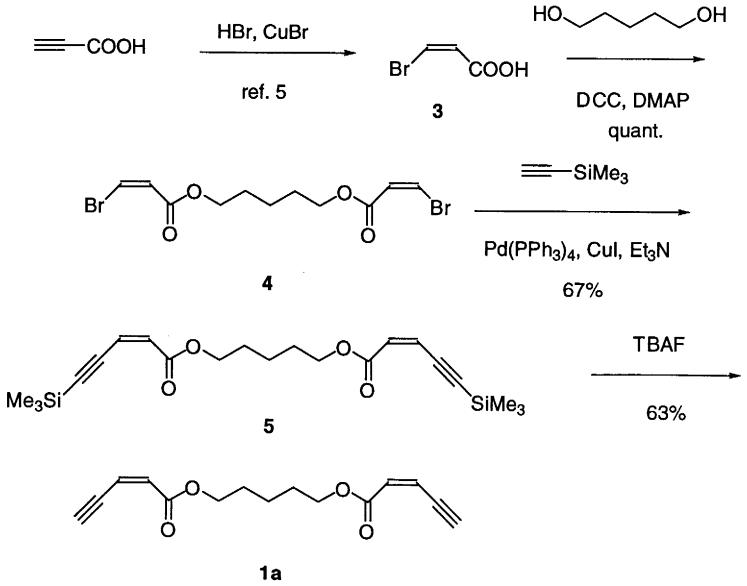


(4)

metacyclophanes

Bisenyne **1a** was prepared in four steps from propiolic acid (Scheme 1). Thus, (*Z*)-2-bromoacrylic acid **3** was prepared by the CuBr-catalyzed addition of HBr to propiolic acid,[5] and the acid was treated with 1,5-pentanediol in the presence of DCC–DMAP to yield the bisester **4** in quantitative yield. Sonogashira coupling of **4** with trimethylsilyl acetylene proceeded smoothly to give the protected bisenynes **5** in 67% yield. Compound **5** was deprotected by TBAF to give the bisenyne **1a** in 63% yield. Other enynes (**1b**–**e**) were similarly prepared by using the corresponding diols.

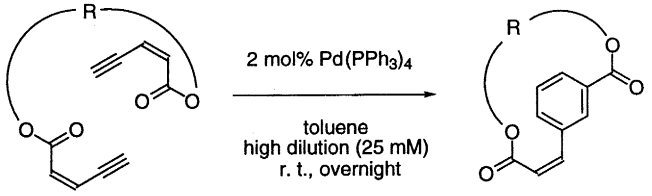


Scheme 1.

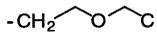
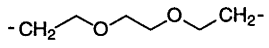
The bisenynes **1** cyclized in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give the metacyclophanes **2** in good to excellent yields, and the results are summarized in Table 1. Thus, **1a** cyclized under

dilute condition (25 mM, in toluene) to give the metacyclophane **2a** in excellent yield (entry 1). The reaction of **1b** and **1c**, which have a longer carbon chain and shorter carbon chain, respectively, proceeded smoothly, and the products **2b** and **2c** were isolated in high yields (entries 2 and 3). The polyoxometacyclophanes **2d** and **2e** were prepared in good yields from the corresponding acyclic analogues **1d** and **1e**, respectively (entries 4 and 5). This result indicates that various functional groups will be easily introduced to the side chain of these cyclophanes. These compounds are novel crown ether analogues and might be attractive as ionophores. The reactivity of **1a**–**e** was significantly higher compared to those of other alkyl enynes,[2,3] and the reaction proceeded smoothly even at room temperature in a highly regioselective manner: isomeric compounds such as paracyclophanes were not isolated.[6]

Table 1
Intramolecular benzannulation of bisenynes



1 **2**

entry	enyne	R	product	isolated yield (%)
1	**1a**	-$(CH_2)_5$-	**2a**	92
2	**1b**	-$(CH_2)_8$-	**2b**	70
3	**1c**	-$(CH_2)_4$-	**2c**	85
4	**1d**		**2d**	65
5	**1e**		**2e**	68

A typical experimental procedure is as follows: to a yellow solution of $Pd(PPh_3)_4$ (2.5 mg, 2 μmol) in dry toluene (4 mL) was added **1a** (26 mg, 100 μmol) at room temperature and the mixture was stirred overnight under Ar. The mixture was passed through a short column packed with silica gel and evaporated. The residue was further purified by column chromatography (eluent hexane–EtOAc) to give **2a** (24 mg, 92%).[7]

In summary, we succeeded in a short synthesis of metacyclophanes using intramolecular benzannulation of highly reactive bisenynes. Functionalized metacyclophanes, such as the polyoxometacyclophanes, were easily prepared by attaching appropriate functional groups into the bisenyne tether.

References

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4. Saito, S.; Tsuboya, N.; Chounan, Y.; Nogami, T.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 7529–7532.
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6. Under these highly dilute conditions, no dimeric compounds or polymeric compounds were isolated. When we carried out these reactions at higher concentration, the formation of the polymer was observed.
7. Spectroscopic data of **2a**: ^{1}H NMR δ 8.53 (s, 1H), 7.98–7.95 (m, 1H), 7.48–7.43 (m, 2H), 6.79 (d, 1H, *J*=12.9 Hz), 6.04 (d, 1H, *J*=12.9 Hz), 4.40–4.34 (m, 4H), 1.89–1.83 (m, 6H); ^{13}C NMR 167.9, 165.9, 135.6, 134.7, 133.9, 130.7, 130.0, 129.5, 128.8, 122.1, 64.9, 63.2, 26.8, 25.5, 22.0; IR (neat) 2957, 1724, 1712, 1279, 1265, 1221, 1194, 762, 687 cm^{-1}; HRMS calcd for $C_{15}H_{16}O_4$: 260.1048. Found: 260.1042. Compound **2d**: ^{1}H NMR δ 8.69 (s, 1H), 7.94–7.91 (m, 1H), 7.45–7.43 (m, 2H), 6.86 (d, 1H, *J*=12.9 Hz), 6.01 (d, 1H, *J*=12.9 Hz), 4.51–4.40 (m, 4H), 3.84–3.76 (m, 4H); ^{13}C NMR 167.3, 167.0, 137.3, 134.6, 134.1, 131.4, 131.1, 129.56, 128.6, 121.4, 69.6, 68.3, 64.3, 63.4; IR (neat) 2988, 2955, 2926, 2876, 1717, 1273, 1202 cm^{-1}; HRMS calcd for $C_{14}H_{15}O_5$: 262.0840. Found: 262.0834. Other products were characterized similarly.