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Synthesis of Strained Pyridine-Containing Cyclyne via Reductive Aromatization

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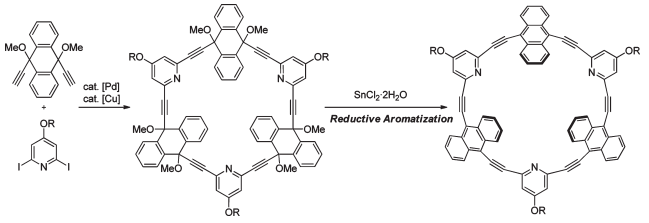
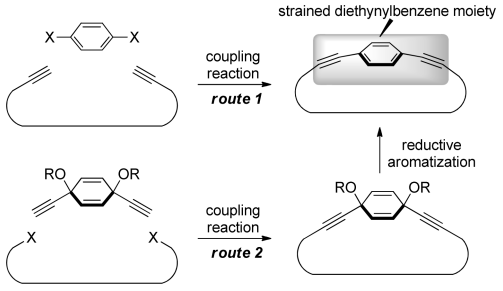


The Sonogashira−Hagihara coupling reactions of 2,6-diiodopyridine and *cis*-3,6-diethynyl-3,6-dimethoxycyclohexa-1,4-diene or *cis*-9,10-diethynyl-9,10-dimethoxy-9,10-dihydroanthracene gave macrocyclic compounds having alternating 2,6-diethynylpyridine and 3,6-dimethoxycyclohexa-1,4-diene segments. Transformation of the C_3-symmetric 2,6-diethynylpyridine-based cyclotrimer was efficiently achieved using tin-mediated reductive aromatization under mild conditions.

Strained macrocyclic π-conjugated molecules containing *p*-phenylene and *p*-phenyleneacetylene segments have received considerable attention due to their attractive structural features in material chemistry as well as host−guest chemistry.[1] Because of their strained structures, the simple cross-coupling reactions as a final step are not applicable to the synthesis of constrained skeletons involving *p*-phenyleneacetylene segments (Scheme 1, route 1). Therefore, several synthetic approaches including bromination−debromination,[2] photochemical valence isomerization,[3] laser-induced or photochemical cycloreversion,[4] reduction using lithium naphthalenide,[5] dehydration−oxidation,[6] and reductive elimination of diarylmetal species[7] have been developed to construct strained macrocycles composed of bent benzene rings or bent acetylene moieties. However, almost all of these transformations require harsh conditions. Meanwhile, Lewis acid mediated reductive aromatization is a well-known method for constructing benzene rings from cyclohexa-1,4-dienes under mild conditions with high efficiency.[8,9] Swager and co-worker have achieved the elegant synthesis of poly(anthrylenebutadiynylene)s using same tin-mediated reductive aromatization approach.[10] Based on the results of previous studies, we focused our attention on tin-mediated reductive aromatization to construct strained π-conjugated macrocycles (Scheme 1, route 2).

SCHEME 1. Synthetic Approaches To Construct Strained Diethynylbenzene-Containing Macrocycles



Pyridine-containing π-conjugated systems have attracted much attention because of their electron-deficient properties and their coordinative character.[11] The 2,6-diethynylpyridine

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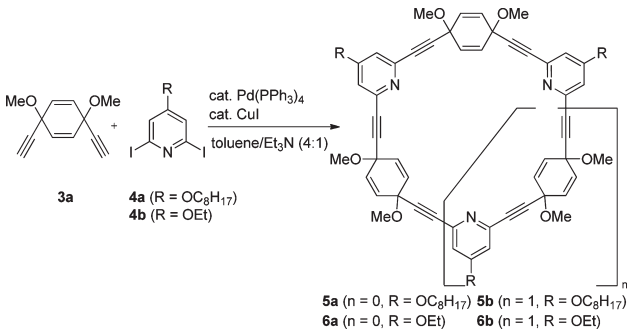
TABLE 1. Synthesis of Pyridine-Containing Macrocycles 5 and 6



entry	[Pd]/[Cu] (mol%/mol%)	concn (M)	time (d)	products and isolated yields[a] (%)			
1	2.5/10	0.01	1	**5a**	7	**5b**	10
2	2.5/10	0.02	1	**5a**	5	**5b**	9
3	2.5/10	0.04	1	**5a**	3	**5b**	8
4	2.5/10	0.01	2	**5a**	9	**5b**	13
5	0.6/2.5	0.02	3	**5a**	10	**5b**	11
6	2.5/10	0.02	1	**6a**	7	**6b**	9

[a]Isolated yields based on the repeating segment in the brace.

unit is an attractive building block for pyridine-containing π-conjugated systems, such as strong fluorescence-emitting cyclyne **1**[12] (Φ_{rel} = 0.59) and poly(*meta*-ethynylpyridines) that can selectively form helical structures with saccharides (Figure 1).[13] Despite these attractive features of diethynylpyridine-containing π-conjugated compounds, synthesis of the smaller and more strained cyclyne **2** has not been reported so far because of the synthetic difficulties in cross-coupling approaches. In this paper, we report the synthesis of a strained pyridine-containing cyclyne using mild and efficient tin-mediated reductive aromatization.

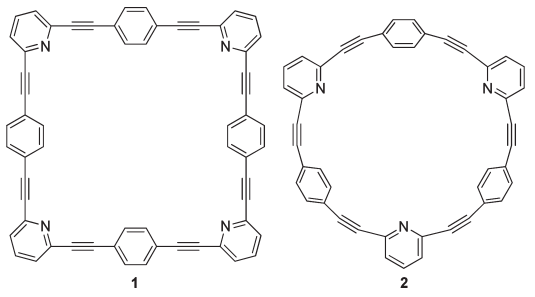


FIGURE 1. Pyridine-containing cyclynes.

First, we tried to prepare cyclic precursors using the Sonogashira−Hagihara coupling reaction to synthesize the target cyclyne **2**. When the coupling reaction of *cis*-3,6-diethynyl-3,6-dimethoxycyclohexa-1,4-diene (**3a**) and 2,6-diiodo-4-octyloxypyridine (**4a**) with catalytic amounts of $Pd(PPh_3)_4$ and CuI in toluene/Et_3N (v/v = 4:1, 0.01 M) was carried out, a mixture of pyridine-containing macrocyclic compounds **5a** (n = 0), **5b** (n = 1), and oligomers was obtained (Table 1, entry 1). The macrocycles **5a** and **5b** were purified using gel permeation chromatography (GPC) with $CHCl_3$ as the eluent. The lower the concentration of the reactants, the higher the yields that were obtained (entries 1−3). In 0.01 M conditions, extension of the reaction time improved yields slightly because of full conversion of short oligomers (entry 4). The reaction with low catalytic loading gave the corresponding products in 10% and 11% yields, respectively, although a longer reaction time was necessary (entry 5). The reaction of **3a** with 4-ethoxyl-2,6-diiodopyridine (**4b**) also gave the corresponding products **6a** (n = 1) and **6b** (n = 2) in 7% and 9% yields, respectively (entry 6). The macrocyclic structures of **5a**, **6a**, and **6b** were determined by X-ray crystal structure analyses of crystals grown from CH_2Cl_2/MeOH (see the Supporting Information). Next, we tried the coupling reaction of *cis*-9,10-diethynyl-9,10-dimethoxy-9,10-dihydroanthracene (**3b**) with 4-octyloxy-2,6-diiodopyridine (**4a**) or 2,6-diiodopyridine (**4c**). The macrocycles **7a** (n = 0), **7b** (n = 1), **8b** (n = 1), and **8c** (n = 1) including 9,10-dihydroanthracene were obtained (Scheme 2).[14] Compared with cyclohexa-1,4-diene **3a**, the coupling reaction of **3b** proceeded slowly. Therefore, a higher reaction temperature was required to obtain the corresponding macrocycles in better yields. Next, we attempted the stepwise synthesis of **7b** from diiodide **9** and diyne **10** to improve the yield, but the yield of macrocycle was comparable to that of the coupling between **3b** and **4b** (13% yield) (Scheme 2).

Having obtained the cyclic precursors **5b**−**8b** containing 2,6-diethynylpyridine moieties, we next attempted the reductive aromatization.[15] First, we carried out the reaction of **5b** and **6b** including cyclohexa-1,4-diene with an excess amount of $SnCl_2$, but we could not purify the corresponding

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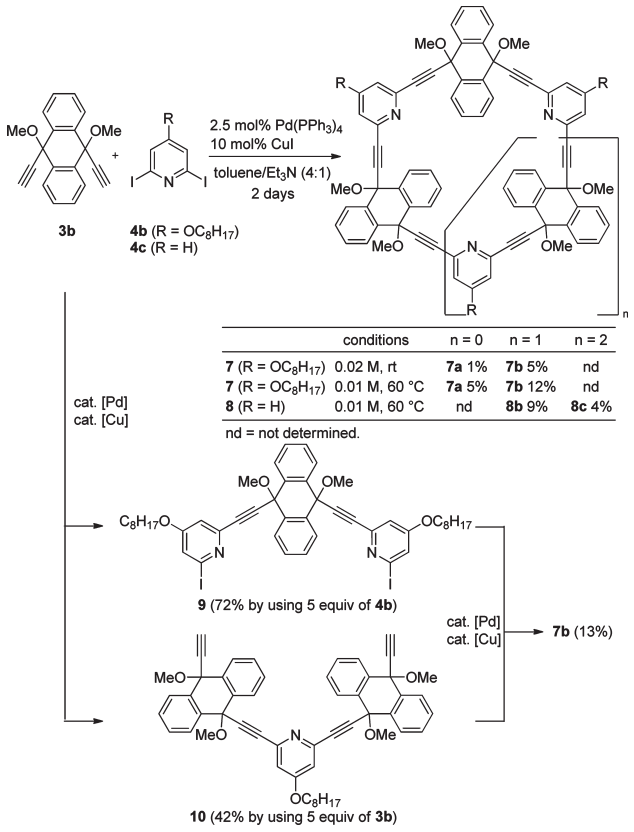
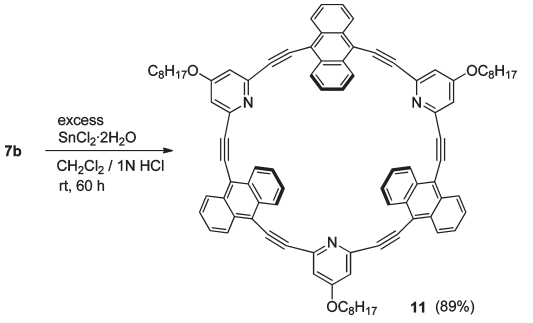
(14) Macrocycle **8a** (R = H, n = 0) was detected by LRMS as well as HRMS, but other spectral data could not be measured because of low solubility in any organic solvents after evaporation. The macrocyclic structure of **8c** was determined by X-ray crystal structure analysis. See the Supporting Information.

(15) The reductive aromatization of **5a**, **6a**, and **7a** (n = 0) did not proceed to give the corresponding cyclynes at all.

SCHEME 2. Synthesis of Pyridine-Containing Macrocycles 7 and 8



SCHEME 3. Reductive Aromatization of 7b



cyclyne from the messy reaction mixtures.[16] In contrast, the reductive aromatization of **7b** proceeded smoothly to give the corresponding cyclyne **11** in excellent yield (Scheme 3).[17] To clarify the structural features of the cyclyne, we performed a DFT calculation on the core structure of **11** (Figure 2).[18] Interestingly, two anthracene rings are twisted against the plane including the core cyclyne skeleton, while the bis(dipyridylethynyl)anthracene unit forms a π-conjugated

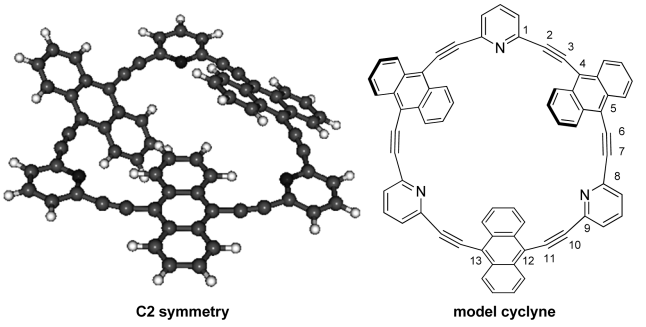


FIGURE 2. Energy-minimized structure of anthracene-containing cyclyne (B3LYP/6-31G(d)). Selected angles: ∠C1−C2−C3 = 168.0°; ∠C2−C3−C4 = 171.4°; ∠C3−C4−C5 = 174.3°; ∠C4−C5−C6 = 173.5°; ∠C5−C6−C7 = 171.7°; ∠C6−C7−C8 = 169.2°; ∠C9−C10−C11 = 167.2°; ∠C10−C11−C12 = 169.8°; ∠C11−C12−C13 = 177.5°.

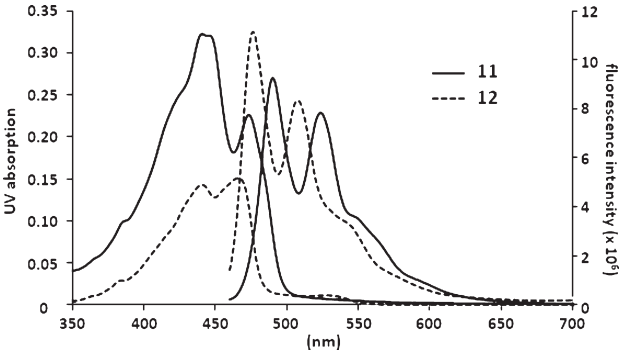
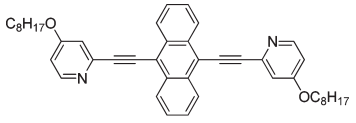


FIGURE 3. UV−vis absorption and fluorescence spectra of **11** (solid line) and **12** (broken line) in $CHCl_3$ solution (1.0×10^{-5} M).

TABLE 2. Optical Properties of 11 and 12[a]

	UV−vis λ_{max} (nm)	ε (L·mol^{-1}·cm^{-1})	PL λ_{max} (nm)[b]	Φ_{abs}[c]
11	441, 446, 474	3.2×10^4	489, 523	0.47
12	439, 467	1.5×10^4	475, 507	0.59

[a] 1.0×10^{-6} M $CHCl_3$ solution were measured. [b] The excitation wavelength was 439 nm in both cases. [c] Determined by using an integrating sphere.



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planar structure. This might be caused by the steric repulsion of three anthracene rings. The angles shown in Figure 2 indicate that both the anthracene rings and the alkynes in the nanoring structure are distorted.

We measured the UV−vis and fluorescence spectra of **11** and the reference compound **12** (Figure 3 and Table 2). The UV−vis absorption spectrum of **11** is almost the same spectrum as **12** with a slightly bathochromic shift.[19] This shows that the absorption bands of **11** are attributed to the bis(dipyridylethynyl)anthracene unit. The bathochromic

(16) Bertozzi et al. also mentioned that the reductive aromatization of cyclohexadiene moieties to synthesize cycloparaphenylenes led to a complex mixture. See ref 5.

(17) The reductive aromatization of **8b** also gave the corresponding cyclyne, but the cyclyne gradually decomposed under the reaction conditions. See the Supporting Information.

(18) Visualized by Molekel. (a) Flukiger, P.; Luthi, H. P.; Portmann, S.; Weber, J. *MOLEKEL 4.3*, Swiss Center for Scientific Computing, Manno, Switzerland, 2000−2002. (b) Portmann, S.; Luthi, H. P. *Chimia* **2000**, *54*, 766–770.

(19) The time-dependent (TD) calculation of the model cyclyne shown in Figure 2 indicates that the UV−vis absorption spectrum of **11** is reasonable. The results of calculation are summarized in the Supporting Information.

shift of the fluorescence spectra of cyclyne **11** would be caused by extension of the π-conjugated structure. The absolute quantum yield of **11**, which was similar to that of **1**, indicates that the strained structure does not affect the quantum efficiency.

In summary, we have demonstrated an efficient tin-mediated reductive aromatization to construct a strained diethynylpyridine-containing π-conjugated cyclyne. The resulting cyclyne **11** emitted strong fluorescence around 500 nm with a good fluorescence quantum yield. Although the efficiencies of macrocyclization using cross-coupling reactions should be improved, the present results support the belief that the reductive aromatization is a potential method to construct strained π-conjugated systems. By using this efficient transformation, the syntheses of cycloparaphenyleneacetylenes as well as heteroaromatic ring-containing cyclynes are currently being investigated in our laboratory.

Experimental Section

The General Procedure for the Synthesis of Macrocycles 5−8 Exemplified by Macrocycle 7. A solution of diyne **3b** (0.24 g, 0.83 mmol) and **4a** (0.38 g, 0.83 mmol) in toluene/Et_3N (v/v = 4:1, 80 mL, 0.01 M) was degassed. To this solution were added CuI (16 mg, 0.084 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.020 mmol) at room temperature. After being stirred for 48 h at 60 °C, the reaction mixture was washed with saturated NH_4Cl aqueous solution. The aqueous solution was extracted with $CHCl_3$ (20 mL × 2), and the combined organic solution was dried over $MgSO_4$. The organic solvents were removed under reduced pressure, and the residue was subjected to short column chromatography on SiO_2 with hexane/AcOEt (v/v = 1:1) to remove polymeric compounds. The organic solvents were removed under reduced pressure, and the residue was subjected to GPC with $CHCl_3$ as an eluent to give macrocycles **7**. **Macrocycle 7a (*n* = 0):** pale yellow solid (20 mg, 0.040 mmol, 5%); mp > 250 °C; IR (KBr) 2925, 2854, 2235 (C≡C), 1585, 1552, 1224, 1113, 1068, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 0.92 (t, J = 6.9 Hz, 3H), 1.32 (m, 10H), 1.79 (m, 2H), 2.71 (s, 6H), 3.97 (t, J = 6.6 Hz, 2H), 6.96 (s, 2H), 7.38 (dd, J = 3.3, 5.8 Hz, 4H), 7.79 (dd, J = 3.3, 5.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 14.0, 22.7, 25.8, 28.8, 29.2, 29.2, 31.8, 50.5, 68.4, 71.2, 84.5, 91.0, 113.2, 128.2, 129.5, 134.4, 143.8, 164.7; HRMS (FAB) calcd for $C_{66}H_{67}N_2O_6$ ($M + H^+$) 983.4999, found 983.4992. **Macrocycle 7b (*n* = 1):** pale yellow solid (48 mg, 0.098 mmol, 12%); mp > 250 °C; IR (KBr) 3435, 2292, 2233 (C≡C), 1582, 1551, 1261, 1095, 802, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 0.90 (t, J = 6.8 Hz, 3H), 1.25 (m, 10H), 1.31 (m, 2H), 2.88 (s, 6H), 3.62 (t, J = 6.3 Hz, 2H), 6.56 (s, 2H), 7.42 (dd, J = 3.6, 5.9 Hz, 4H), 7.89 (dd, J = 3.6, 5.9 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 14.1, 22.6, 25.8, 28.5, 29.1, 29.2, 31.8, 51.2, 68.0, 71.8, 85.4, 90.5, 114.3, 128.2, 129.2, 134.7, 143.6, 164.4; HRMS (FAB) calcd for $C_{99}H_{100}N_3O_9$ ($M + H^+$) 1474.7460, found 1474.7440.

Reductive Aromatization of 7b. To a solution of **7b** (14 mg, 9.0 μmol) in CH_2Cl_2 (8 mL, bubbling of N_2 for 30 min before use) was added a solution of $SnCl_2 \cdot 2H_2O$ (0.60 g, 2.7 mmol, 100 equiv) in aqueous HCl solution (18 mL, 1 N, bubbling of N_2 for 30 min before use) at room temperature in dark. After the reaction mixture was stirred at room temperature for 60 h in the dark, the color changed from pale yellow to red. The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic solution was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried over $MgSO_4$. The organic solvent was removed under reduced pressure, and the crude product was subjected to GPC with $CHCl_3$ as an eluent to give cyclyne **11** (10 mg, 7.8 μmol, 89%) as a redish brown solid: mp > 250 °C; IR (KBr) 2923, 2852, 2187 (C≡C), 1581, 1540, 1434, 1261, 1156, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 0.93 (m, 3H), 1.33 (m, 10H), 1.90 (m, 2H), 4.17 (t, J = 6.6 Hz, 2H), 7.26 (s, 2H), 7.52 (dd, J = 3.5, 6.6 Hz, 4H), 8.85 (dd, J = 3.5, 6.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 14.1, 22.7, 25.9, 28.9, 29.2, 29.4, 29.7, 31.8, 68.7, 89.0, 103.9, 110.7, 118.5, 127.2, 127.4, 132.8, 145.4, 166.1; HRMS calcd for $C_{93}H_{82}N_3O_3$ ($M + H^+$) 1288.6356, found 1288.6375.

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Supporting Information Available: Experimental details, spectroscopic data, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.