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Acetylenic Homocoupling Methodology Towards the Synthesis of 1,3-Butadiynyl Macrocycles: [14_2]-Alleno-Acetylenic Cyclophanes

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[14_2]-Alleno-acetylenic cyclophanes were synthesized through two different approaches: an intermolecular coupling between two alkynyl fragments, and an intramolecular ring-closure of a linear acyclic bisalkynyl oligomer. The symmetry of the target dictates the choice of the most suitable method. To illustrate these approaches we have used 1,3-diethynyl-substituted allenes as building blocks. Due to the stereogenic character of the allene moiety, the alleno-acetylenic cyclophanes were obtained as a mixture of diastereoisomers, and the major twist isomers were resolved by preparative HPLC. The different symmetry of the isomers allowed the assignment of the relative configuration of the major twist isomers by taking into consideration the number of nonequivalent groups in the respective NMR spectra.

Introduction

Functionalized shape-persistent macrocycles, in particular cyclophanes, are intriguing and attractive structures because of their chemical, physiochemical, and biological properties.[1] However, despite the efforts made during the last decades, the synthesis of these compounds remains a challenge. The availability of acetylenic building blocks and the application of modern metal-catalyzed coupling reactions to form sp-sp^2 and sp-sp carbon–carbon bonds have significantly advanced this field.[2]

Generally, alleno-acetylenic macrocycles can be synthesized by either an intermolecular ring closure of bisfunctionalized oligomers,[3] or an intermolecular coupling between two or more ring fragments followed by a unimolecular cyclization.[4] Both strategies have inherent advantages and disadvantages. An intramolecular cyclization guarantees the highest selectivity toward formation of a single cyclic product and, as a result, purification is greatly simplified. Moreover, this approach allows functional groups to be introduced at defined positions of the oligomeric sequence, leading to macrocycles with diverse backbone structures. On the other hand, by using an intermolecular approach, the starting materials can typically be prepared in fewer steps, which often renders this procedure more time efficient. Unfortunately, the probability of forming numerous cyclooligomeric macrocycles is high, making purification of the target molecule difficult.[5]

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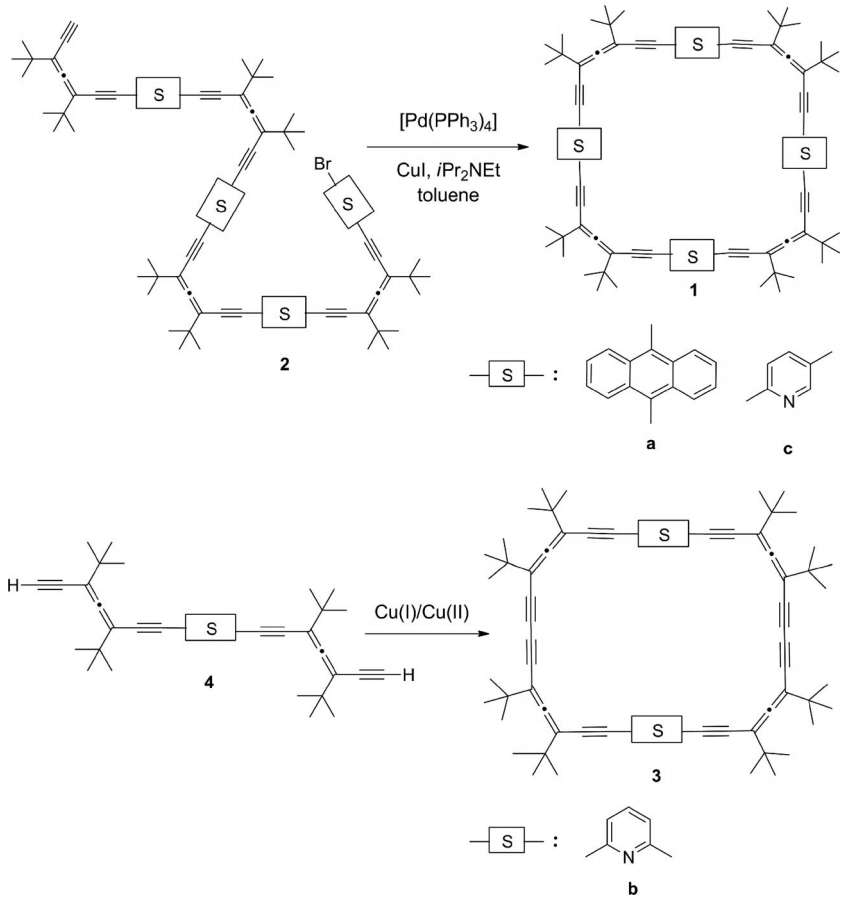
We have previously reported the synthesis of [7_4]-alleno-acetylenic cyclophanes **1a**[4a] and **1c**[4d] through an intramolecular approach, using **2** (Scheme 1) to gain control over the cyclization process and thus avoid the formation of undesired cyclic oligomers. We also obtained [14_2]-alleno-acetylenic cyclophane **3b**[3b] through an intermolecular dimerization.

In our search for an efficient protocol with which to prepare diverse alleno-acetylenic cyclophanes, we compared the efficiency of two alternative approaches, namely inter- and intramolecular ring closures. Here, we present our results regarding the preparation of *twist*-[14_2]-alleno-acetylenic cyclophanes **3** through an intermolecular acetylenic homocoupling between two units of monomer **4** and, as an alternative synthetic method, an intramolecular macrocyclization of bisalkynyl oligomer **5**. Due to the presence of a 1,3-diynyl moiety, we envisaged an oxidative coupling of terminal alkynes as the key step. Both heterotrimer **4** and oligomer **5** can be prepared from commercially available 2,5-, 2,6-dibromopyridine or 9,10-dibromoanthracene through palladium-catalyzed Sonogashira cross-coupling reactions with diethynylallene (±)-**6** (Scheme 2).

Results and Discussion

Intermolecular Approach

The first step towards the preparation of alleno-acetylenic cyclophanes **3** involved the synthesis of racemic diethynylallene [DEA; (±)-**6**]. For this purpose, by following a reported procedure,[6] we prepared DEA (±)-**7a** and **7b** through a Pd-catalyzed S_N2' reaction of pentafluorobenzoate (±)-**8** with acetylenes **9a** and **9b**, respectively. Selective



Scheme 1. Synthesis of alleno-acetylenic cyclophanes **1a**,[4a] **1c**,[4d] and **3b**.[3b]

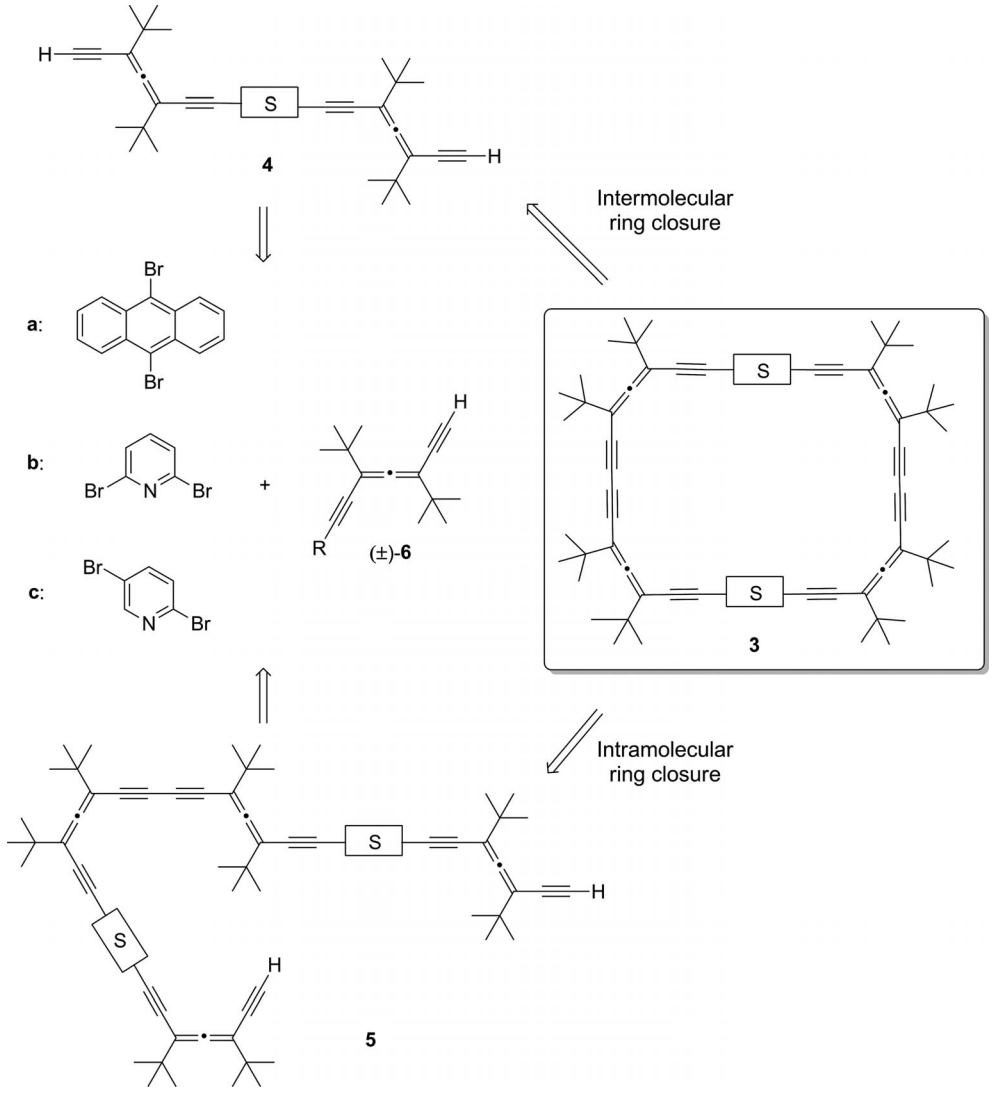
deprotection of these DEAs gave the desired DEA (±)-**6a** and (±)-**6b** in 76 and 67% overall yield, respectively (Scheme 3) (see the Supporting Information for further details).

The synthesis of alleno-acetylenic cyclophanes **3** were carried out by the application of intermolecular acetylenic homocoupling reactions on the respective bisallenoacetylenes **4**, which were prepared by Sonogashira cross-coupling reaction using 2.1 equiv. of monoprotected DEA (±)-**6a** and the appropriate dibromoaromatic spacers in the presence of $[Pd(PPh_3)_2Cl_2]$ and CuI (Scheme 4). Thus, when 9,10-dibromoanthracene or 2,5-dibromopyridine was treated with 2.1 equiv. of (±)-**6a** in the presence of 5 mol-% $[PdCl_2(PPh_3)_2]$, 2 mol-% CuI and Et_3N in CH_3CN at 80 °C, the protected bisallenoacetylene **10a** and **10c** were afforded in 66 and 48% yield, respectively. Subsequent desilylation with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) at 25 °C gave **4a** and **4c**, in 74 and 83% yield, respectively. When 2,6-dibromopyridine was treated with 2.1 equiv. (±)-**6a** in the presence of 2 mol-% $[PdCl_2(PPh_3)_2]$, 5 mol-% CuI, and tetramethylethylenediamine (TMEDA) in toluene at 110 °C followed by desilylation with TBAF in THF at 25 °C, **4b** was obtained in 74% overall yield.[3b]

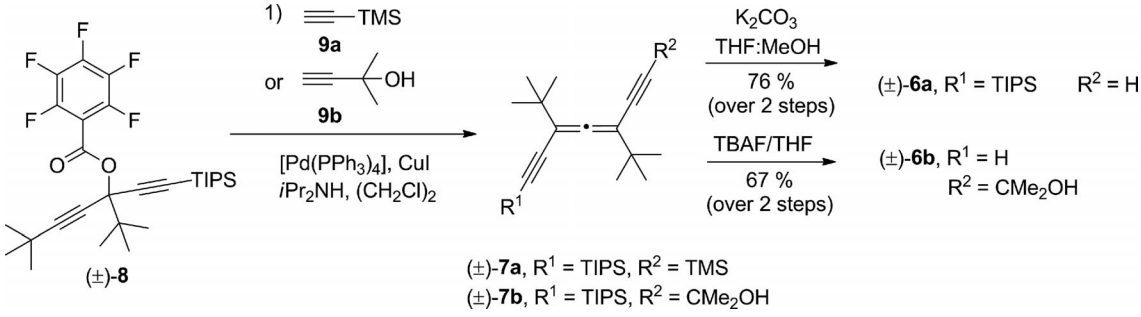
With heterotrimers **4** in hand, we investigated the formation of the 1,3-diynyl moieties. Among the available oxidative homocoupling reactions, modifications of the conventional Glaser method[7] such as Hay [CuCl, TMEDA, O_2, $(CH_2)_2Cl_2$],[8] Eglinton and Galbraith ($CuSO_4$, pyridine, MeOH),[9] and Breslow (CuCl, $CuCl_2$ oxygen-free pyridine)[10] have been most often used for the preparation of macrocycles containing buta-1,3-diyl units. More recently, the use of Pd^{II} as cocatalyst in the presence of Cu^{I} and O_2 has emerged as an alternative to the traditional Cu^{I}/Cu^{II} homocoupling-based methods.[11]

The bisallenoacetylenes **4a**, **4b**, and **4c** were subjected to three different macrocyclization reaction conditions, namely Breslow, and modified Hay conditions, and Pd/Cu-catalyzed homocoupling reaction; the results are summarized in Table 1.

When Hay conditions were employed, namely, addition of deprotected bisacetylenes **4a**, **4b** or **4c** under pseudo-high-dilution to a solution of CuI and the bidentate ligand TMEDA in dichloroethane under an O_2 atmosphere, 2,6-pyrido-allenoacetylenic **4b** gave the desired macrocycle **3b** in 68% yield along with other compounds that were identified by mass spectroscopy analysis as the diiodo compound **11b** and the diiodo oligomer **12b** (Figure 1).[3b] This result was not reproducible and, in practically all cases, only the diiodo compounds were obtained. The formation of these iodide compounds, also observed for **4a** and **4c**, could be due to reductive elimination across Cu^{II} species.[12]



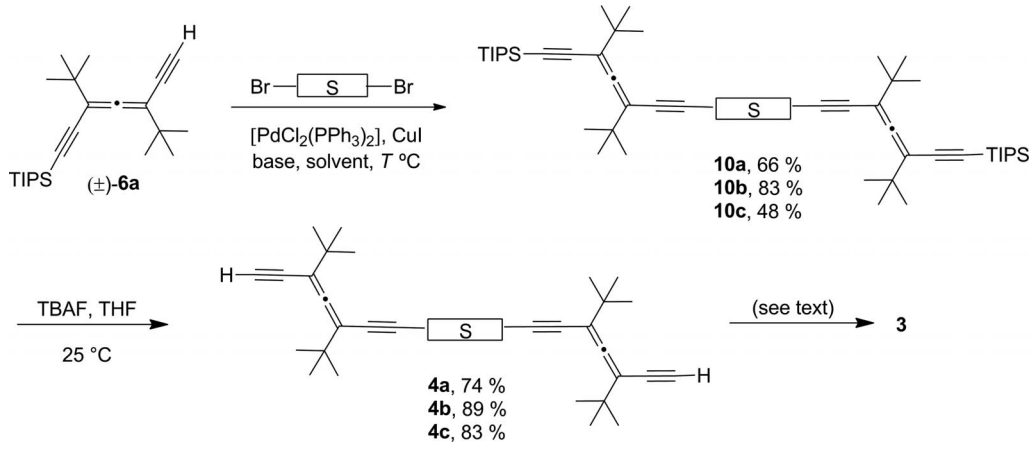
Scheme 2. Retrosynthetic analysis of [14_2]-alleno-acetylenic cyclophanes **3**.



Scheme 3. Synthesis of DEA (±)-**6a** and (±)-**6b**.

Synthesis of **3a**–**c** was then carried out under Pd/Cu-catalyzed homocoupling conditions. Solutions of the heterotrimers **4a**–**c** in toluene were added under pseudo-high-dilution to a solution of CuI, [$Pd(PPh_3)Cl_2$] and TMEDA in toluene under air atmosphere at 60 °C to give, in the case of **4a**, the desired alleno-acetylenic cyclophanes **3a** in good yield (63%) along with traces of a larger [14_3] macrocycle **13a**. Compounds **4b**[3b] and **4c** (Figure 1) gave the corresponding cyclophanes **3b** and **3c**, respectively, as diastereoisomeric mixtures in 56% yield.

Finally, when the reactions were run under Breslow conditions, that is, bisallenoacetylenes **4a**–**c** were treated with CuCl (75 mol-%) and $CuCl_2$ (11 mol-%) in oxygen-free pyridine at 25 °C under pseudo-high-dilution, the correspond-



Scheme 4. Intermolecular approach. Synthesis of alleno-acetylenic cyclophanes **3**.

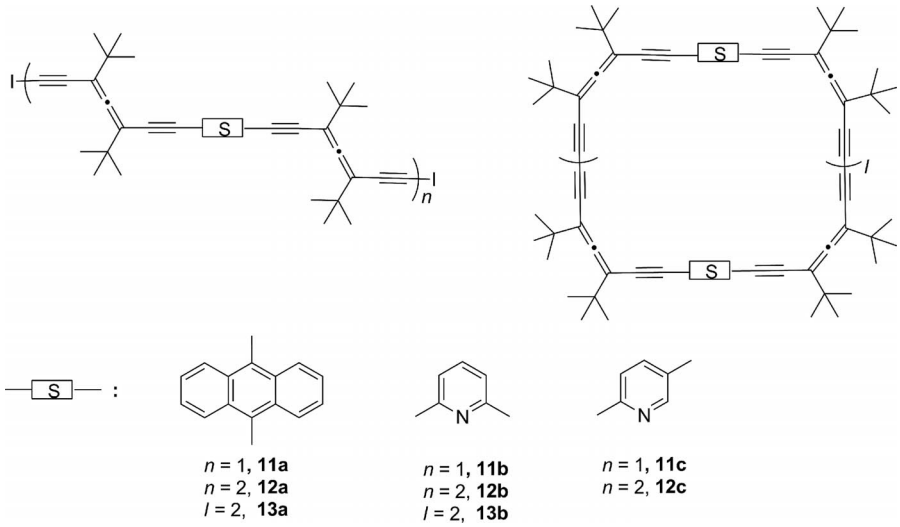


Figure 1. Side products: diiodinated derivatives **11** and **12**, and [14_3]-alleno-acetylenic cyclophane **13**. The compounds were obtained as diastereoisomeric mixtures.

Table 1. Reaction conditions for macrocyclization of **4a**, **4b**, and **4c**.[a]

Reaction conditions	Yield [%]		
	3a	**3b**	**3c**
Hay[b]	–	–[e]	trace
Pd/Cu[c]	63	56	56
Breslow[d]	58	63	54

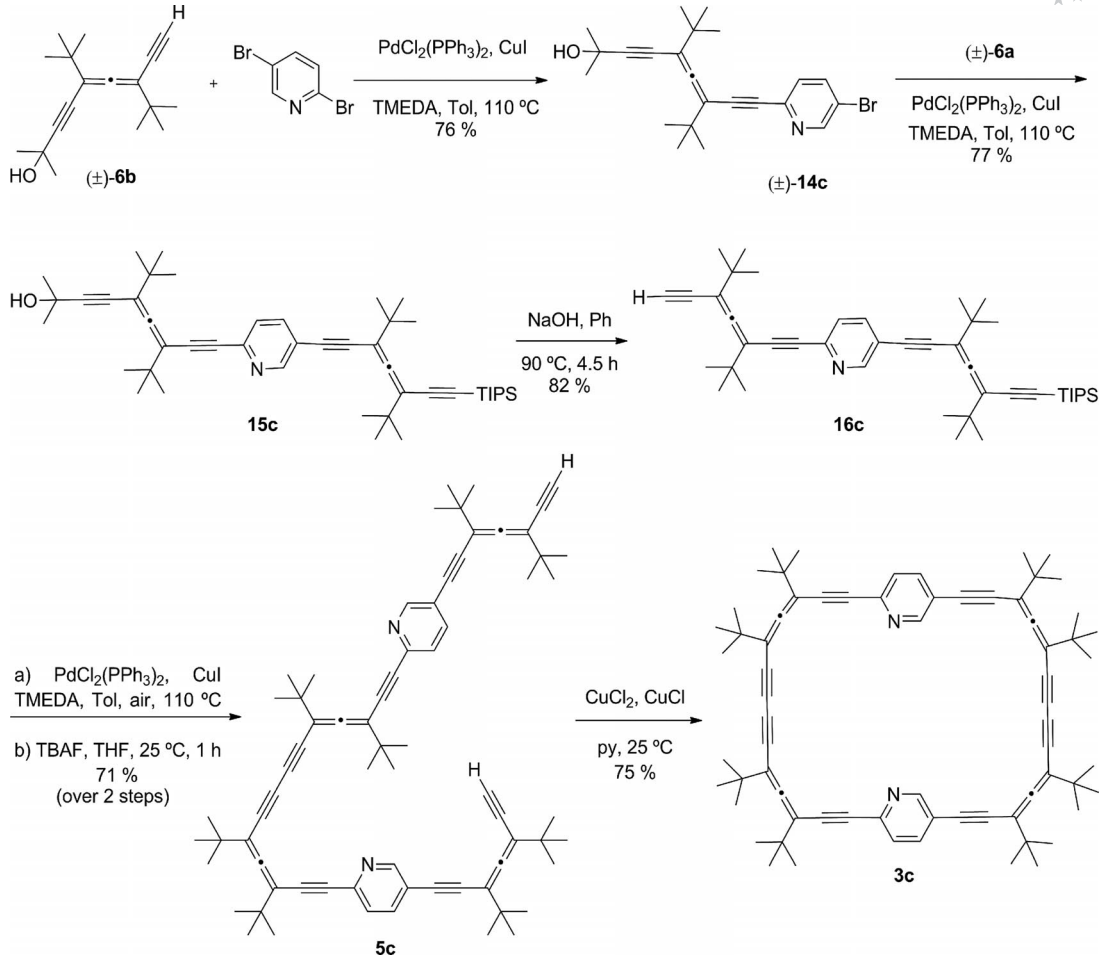
[a] The alleno-acetylenic cyclophanes were obtained as diastereoisomeric mixtures. [b] Hay reaction conditions: CuI, TMEDA, $(CH_2)_2Cl_2$, 25 °C, air. [c] Pd/Cu catalyzed homocoupling reaction conditions: CuI, $[Pd(PPh_3)Cl_2]$, TMEDA, toluene, 60 °C, air. [d] Breslow reaction conditions: CuCl, $CuCl_2$, pyridine, 25 °C, Ar. [e] Not reproducible.

ing cyclophanes **3** were obtained in good yields (58, 63, and 54% for **3a**, **3b**,[3b] and **3c**, respectively). Compound **3a** was obtained along with traces of **13a** (Figure 1), as revealed by its mass spectrum. Due to the nonequivalent reactive positions of **4c**, **3c** was obtained as a mixture of regioisomers. In fact NMR spectroscopic analysis showed a very complex set of signals.

Intramolecular Approach

With the results of the intermolecular approach in hand, we proceeded with the synthesis of alleno-acetylenic cyclophanes **3** through an intramolecular macrocyclization. In the case of alleno-acetylenic cyclophanes **3a** and **3b**, for which the two reactive positions are equivalent, the intermolecular approach may be appropriate. However, for precursors bearing nonequivalent reactive positions, such as bisallenoacetylene **4c**, it is highly likely that performing the reaction in an intermolecular manner would lead to the corresponding cyclophanes as a mixture of regioisomers. In contrast, the intramolecular synthesis of **3c** precludes the formation of the C_2 symmetric regioisomer.

Thus, the synthesis of **3c** through a stepwise intramolecular approach started with two regioselective Sonogashira cross-coupling reactions between 2,5-dibromopyridine and the two different diethynylallenes, first (±)-**6b**, which gave monoallenoacetylene **14c**, and then (±)-**6a** to render the asymmetrically disubstituted hetero-oligomer **15c** in 58% overall yield. Selective deprotection of the acetonide group



Scheme 5. Intramolecular approach. Synthesis of alleno-acetylenic cyclophanes **3c** as a mixture of diastereoisomers.

by reaction with anhydrous NaOH in benzene gave **16c**[4d] in 82% yield. Acetylenic oxidative coupling under an air atmosphere and subsequent deprotection of both TIPS groups with TBAF in THF at 25 °C led to the precursor of macrocycle **5c** in 71% overall yield. A very successful intramolecular ring-closing of **5c** under treatment with CuCl and $CuCl_2$ in pyridine at 25 °C for 1 h (Breslow conditions) afforded the desired 2,5-pyridoalleno-acetylenic cyclophanes **3c** in 75% yield regioselectively (Scheme 5).

Characterization of Twist-alleno-acetylenic Cyclophanes 3a, 3b and 3c

We have shown in our previous work that the diastereoisomeric mixtures can be resolved by using HPLC and characterized, in some cases, by symmetry analysis of the NMR spectra. Again here, the use of the allene as racemate gave alleno-acetylenic cyclophanes **3** as diastereoisomeric mixtures (see Table 2), in which formation of the (*P*,*M*,*M*,*M*)/(*M*,*P*,*P*,*P*)-twist isomers is statistically favored over the formation of the others. As an illustration, the AM1 geometries of **3c** diastereoisomers are included in the Supporting Information. The optimized geometries of the different

Table 2. Nonequivalent groups for the different isomers of alleno-acetylenic cyclophanes **3a**–**c**.[a]

	Isomer	C=**C**=C[b]	*t*Bu[c]
3a	**Twist** (*P*,*M*,*M*,*M*)/(*M*,*P*,*P*,*P*)	4	8[d]
	Crown (*P*,*P*,*P*,*P*)/(*M*,*M*,*M*,*M*)	1	2
	Chair (*P*,*M*,*M*,*P*)	1	2
	Boat (*P*,*M*,*P*,*M*)	1	2
	Couch (*P*,*P*,*M*,*M*)	1	2
3b	**Twist** (*P*,*M*,*M*,*M*)/(*M*,*P*,*P*,*P*)	4	8[e]
	Crown (*P*,*P*,*P*,*P*)/(*M*,*M*,*M*,*M*)	1	2[e]
	Chair (*P*,*M*,*M*,*P*)	1	2[e]
	Boat (*P*,*M*,*P*,*M*)	1	2[e]
	Couch (*P*,*P*,*M*,*M*)	1	2[e]
3c	**Twist-1** (*P*,*M*,*M*,*M*)/(*M*,*P*,*P*,*P*)	4	8[e]
	Twist-2 (*M*,*P*,*M*,*M*)/(*P*,*M*,*P*,*P*)	4	8[e]
	Crown (*M*,*M*,*M*,*M*)/(*P*,*P*,*P*,*P*)	2	4
	Chair (*P*,*P*,*M*,*M*)	2	4
	Boat (*P*,*M*,*P*,*M*)	2	4
	Couch (*P*,*M*,*M*,*P*)/(*M*,*P*,*P*,*M*)	2	4

[a] All diastereoisomers of **3** can present different conformations. [b] Number of nonequivalent cummulenic carbon atoms in the ^{13}C NMR spectra. [c] Number of nonequivalent *tert*-butyl protons in the ^{1}H NMR spectra. [d] Not characterized due to photochemical isomerization. [e] Isolated and characterized.

twist isomers for each alleno-acetylenic cyclophane are depicted in Figure 2.

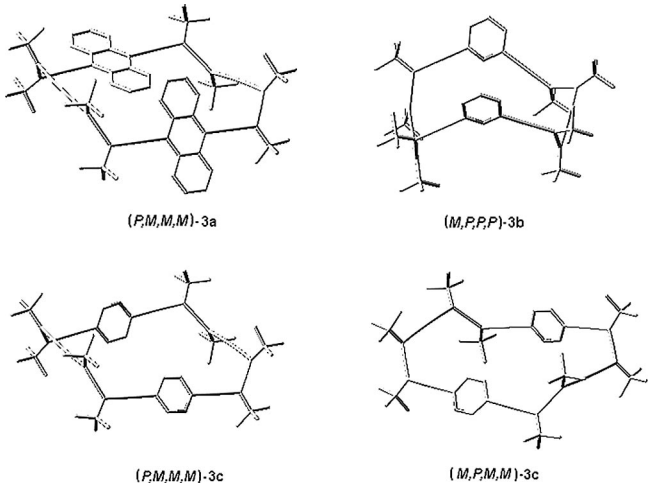


Figure 2. Tube models of geometries optimized at the AM1 level of theory. Top: *twist* (*P*,*M*,*M*,*M*)-**3a** and (*M*,*P*,*P*,*P*)-**3b**; bottom: *twist*-1 (*P*,*M*,*M*,*M*)-**3c** and *twist*-2 (*M*,*P*,*M*,*M*)-**3c**. Only one of the enantiomers of each racemate is depicted.

The different number of chemically nonequivalent groups in the NMR spectra allowed the twist-symmetrical diastereoisomers of these cyclophanes to be distinguished (Table 2). Whereas **3a** and **3b** showed only one twist isomer, **3c** showed two, *twist*-1 and *twist*-2, due to the asymmetry around the nitrogen of the pyridine rings.

Our next goal was to isolate and characterize the major diastereoisomers of all cyclophanes **3**. Thus, the mixtures were resolved by preparative HPLC on the stationary phase "Buckyclutcher 1" (for more details see the Supporting Information).[13] Because of its fast isomerization to the original diastereomeric mixture probably due to the presence of the anthracene unit favoring photochemical isomerization at low UV energies, the major compound for **3a**, *twist*-**3a**, was not isolated in pure form.[14] The major compound was successfully isolated in pure form and fully characterized for *twist*-**3b**,[3b] *twist*-1-**3c** and *twist*-2-**3c**.

Conclusions

We have shown using the synthesis of alleno-acetylenic cyclophanes **3** the utility of both intra- and intermolecular ring-closing processes in oxidative acetylenic homocoupling reactions. Choosing one or the other depends on the symmetry of the target system: in the case of symmetrical spacers (**a** and **b**), the intermolecular approach should be preferred because it involves fewer steps and proceeds in good overall yields. On the other hand, for unsymmetrical spacers (**c**), the intramolecular approach is preferred because it avoids the formation of regioisomeric products. In this way, cyclophane **3c** was obtained with total regioselectivity in good yield. HPLC resolution along with NMR experiments allowed the major diastereomers of **3** to be characterized as the twist isomers.

Experimental Section

Materials and General Methods: Reagents and solvents were purchased as reagent grade and used without further purification unless stated otherwise. THF was freshly distilled from sodium benzophenone ketyl; $(CH_2)_2Cl_2$, amines, and pyridine were freshly distilled from CaH_2. All reactions were performed in oven- or flame-dried glassware under an inert atmosphere of argon unless stated otherwise. Chromatography refers to flash chromatography (FC) on SiO_2 60 (230–400 mesh) from Merck; a head pressure of around 0.2 bar was applied. TLC was performed on UV_{254} SiO_2-coated plates from Merck with visualization by UV light (254 nm). HPLC: Waters 510 pump controlled by PMC pump controller, with U6K injector and UV detector. Solvents were HPLC grade and degassed with He. UV/Vis spectra were recorded with a Varian-CARY 100 Bio Scan or a 500 Scan spectrophotometer with a 1 cm cell at 25 °C. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded with Bruker 600 MHz, Bruker 500 MHz, Bruker 400 MHz, or Varian Gemini 300 MHz spectrometers at 298 K with residual solvent peaks as internal reference; chemical shifts are reported in δ (ppm) and coupling constants J are given in Hz. The multiplicities are expressed as follows: s singlet, d doublet, t triplet, m multiplet. IR spectra were recorded with a JASCO FT/IR-4200 infrared spectrometer; peaks are quoted in wavenumbers (cm^{-1}). Mass spectra were recorded at the Cacti Universidade de Vigo with a Hewlett–Packard HP59970 instrument operating at 70 eV by electron ionization and with an APEX III FT-ICR MS (Bruker Daltonics, Billerica, MA) equipped with a 7 T actively shielded magnet. High-resolution mass spectra were recorded with a VG Autospec instrument. Elemental analyses were performed with a Fisons EA-1108. See the Supporting Information for further details.

Computational Methods: Structures for all diastereoisomers of cyclophane **3c** were first optimized in vacuo by using the OPLS 2005 force field[15] as implemented in the MacroModel program. Although the macrocycles present a very rigid skeleton, some conformational mobility is present due to the rotation of the pyridine rings. Hence, a short Monte Carlo conformational search was performed for each of the diastereoisomers. As expected, the found rotamers were nearly degenerate in energy. In the case of the symmetric diastereoisomers, the lowest energy rotamers close to maximum symmetry structures were chosen and symmetrized by using the SYMMOL program.[16] The geometries so obtained were reoptimized in vacuo at the semiempirical AM1[17] level of theory by using the Gaussian09 program.[18] AM1 geometries were also computed for **3a** and **3b** major twist isomers. Frequencies were analytically computed to verify the nature of the obtained stationary points as minima.

9,10-Bis[3,5-di(*tert*-butyl)-7-(triisopropysilyl)hepta-3,4-diene-1,6-diynyl]anthracene (10a): Two solutions were prepared: (1) A solution of (±)-**6a** (50 mg, 0.14 mmol) and Et_3N (30 μL, 0.20 mmol) in CH_3CN (2.0 mL) in a Schlenk tube; (2) A solution of $[PdCl_2(PPh_3)_2]$ (2 mg, 0.003 mmol) and 9,10-dibromoanthracene (21 mg, 0.06 mmol) in CH_3CN (1.0 mL). Both solutions were degassed with Ar. CuI (0.23 mg, 1.2 μmol) was added to Solution 2, which was further degassed with Ar. Solution 2 was transferred by cannula to Solution 1. After sparging the reaction, it was stirred and heated to reflux (80 °C) under Ar for 12 h. The reaction mixture was then filtered through silica gel with hexane and the solvent was removed under reduce pressure. Purification by FC on silica gel (hexane) afforded **10a** (41 mg, 66%) as a brown solid. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.55 (dd, J = 6.7, 3.2 Hz, 4 H), 7.58 (dd, J = 6.7, 3.2 Hz, 4 H), 1.37 (s, 18 H, *t*Bu), 1.27 (s, 18 H, *t*Bu), 1.12 (s, 42 H, TIPS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 212.8

(2 C, C=*C*=C), 131.9 (4 C), 127.2 (4×CH), 126.5 (4×CH), 118.6 (2 C), 104.0 (2 C), 103.7 (2 C), 100.1 (2 C), 96.5 (2 C), 94.6 (2 C), 89.5 (2 C), 35.8 (2 C, *t*Bu), 35.7 (2 C, *t*Bu), 29.5 (6×CH_3, *t*Bu), 29.2 (6×CH_3, *t*Bu), 18.8 (12×CH_3, TIPS), 11.5 (6×CH, TIPS) ppm. MALDI-MS: *m*/*z* = 910 (56) [M + Na]$^+$, 887 (48) [M$^+$], 830 (100) [M – Me_3C]$^+$. HRMS (MALDI): calcd. for $C_{62}H_{86}Si_2^+$ [M]$^+$ 886.6268; found 886.6229. IR (neat): $\tilde{\nu}$ = 2960, 2863, 2139, 1460, 1437, 1361, 1243, 1094, 1017, 995, 882, 764, 740, 676 cm^{-1}. $C_{62}H_{86}Si_2$ (887.5): calcd. C 83.90, H 9.77, Si 6.33; found C 83.76, H 9.76. UV/Vis (hexane): λ_{max} (ε, L mol^{-1} cm^{-1}) = 221 (67400), 271 (105500), 304 (27800), 431 (34800), 457 (42100) nm. Fluorescence spectrum (hexane, λ_{ex} = 315 nm): λ_{max} = 468, 500 nm; *f* = 0.51.

2,5-Bis[3,5-di(*tert*-butyl)-7-(triisopropysilyl)hepta-3,4-diene-1,6-diynyl]pyridine (10c): Two solutions were prepared: (1) A solution of (±)-**6a** (50 mg, 0.14 mmol) and Et_3N (30 μL, 0.20 mmol) in CH_3CN (2.0 mL) in a Schlenk tube; (2) A solution of [$PdCl_2$-(PPh_3)$_2$] (2 mg, 3.5 μmol) and 2,5-dibromopyridine (16 mg, 0.07 mmol) in CH_3CN (1.0 mL). Both solutions were degassed with Ar. CuI (0.3 mg, 1.4 μmol) was added to Solution 2 and oxygen-containing air was purged out with Ar. Solution 2 was transferred by using a cannula to Solution 1. After sparging the reaction mixture, it was stirred and heated to reflux (80 °C) under Ar for 6 h. The solvent was then removed under vacuum and the crude material was partitioned between 0.45 M aqueous KCN solution and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by FC on silica gel (hexane/CH_2Cl_2, 7:2) afforded **10c** (27 mg, 48%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.62 (dd, *J* = 2.1, 0.8 Hz, 1 H), 7.67 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.39 (dd, *J* = 8.1, 0.8 Hz, 1 H), 1.21 (s, 9 H, *t*Bu), 1.19 (s, 9 H, *t*Bu), 1.18 (s, 9 H, *t*Bu), 1.17 (s, 9 H, *t*Bu), 1.09 (s, 21 H, TIPS), 1.08 (s, 21 H, TIPS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 212.7 (C, C=*C*=C), 212.3 (C, C=*C*=C), 152.0 (CH), 141.9 (C), 138.0 (CH), 126.3 (CH), 119.5 (C), 104.4 (C), 104.3 (C), 102.5 (C), 102.2 (C), 99.8 (C), 99.7 (C), 94.84 (C), 94.77 (C), 91.6 (C), 89.0 (C), 88.3 (C), 85.4 (C), 35.93 (C, *t*Bu), 35.89 (C, *t*Bu), 35.52 (C, *t*Bu), 35.50 (C, *t*Bu), 29.19 (3×CH_3, *t*Bu), 29.15 (3×CH_3, *t*Bu), 29.01 (3×CH_3, *t*Bu), 28.99 (3×CH_3, *t*Bu), 18.8 (12×CH_3, TIPS), 11.5 (6×CH, TIPS) ppm. MALDI-MS: *m*/*z* = 789 (100) [M + H]$^+$, 775 (30), 745 (29) [M – Me_2HC]$^+$, 732 (25) [M + HMe_3C]$^+$. HRMS (MALDI): calcd for $C_{53}H_{82}NSi_2^+$ [M]$^+$ 788.5980; found 788.5972. IR (NaCl): $\tilde{\nu}$ = 2961, 2864, 2210, 2140, 1737, 1581, 1540, 1463, 1361, 1218, 1103, 1072, 1016, 995, 882, 839, 752, 720 cm^{-1}. UV/Vis (hexane): λ_{max} (ε, L mol^{-1} cm^{-1}) = 222 (43000), 233 (39500), 245 (28000), 329 (52000), 339 (41700) nm.

9,10-Bis[3,5-di(*tert*-butyl)hepta-3,4-diene-1,6-diynyl]anthracene (4a): To a solution of **10a** (100 mg, 0.11 mmol) in anhydrous THF (15.0 mL), TBAF (1 M in THF, 60 μL, 0.06 mmol) was added under Ar and the mixture was stirred for 1 h at 25 °C. The reaction mixture was partitioned between saturated aq. NH_4Cl solution and hexane. The aqueous phase was extracted with hexane, the combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by FC on silica gel (hexane/CH_2Cl_2, 80:20) afforded **4a** (48 mg, 74%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.54 (dd, *J* = 6.6, 3.3 Hz, 4 H), 7.60 (dd, *J* = 6.6, 3.3 Hz, 4 H), 3.09 (s, 2 H, C≡CH), 1.39 (s, 18 H, *t*Bu), 1.28 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 212.7 (2 C, C=*C*=C), 132.0 (4 C), 127.1 (4×CH), 126.7 (4×CH), 118.7 (2 C), 104.6 (2 C), 102.6 (2 C), 96.0 (2 C), 90.0 (2 C), 80.8 (2×CH), 77.4 (2 C), 35.7 (2 C, *t*Bu), 35.6 (2 C, *t*Bu), 29.3 (6×CH_3, *t*Bu), 29.0 (6×CH_3, *t*Bu) ppm. MS (FAB): *m*/*z* = 574 (100) [M$^+$], 517 (20) [M – *t*Bu]$^+$. HRMS (FAB): calcd. for $C_{44}H_{46}^+$ [M]$^+$ 574.3600; found 574.3616. $C_{44}H_{46}$ (574.8): calcd. C 91.93, H 8.07; found C 91.90, H 8.22.

2,5-Bis[3,5-di(*tert*-butyl)hepta-3,4-diene-1,6-diyn-1-yl]pyridine (4c): By following the same procedure described for **4a**, to a solution of **10c** (95 mg, 0.12 mmol) in anhydrous THF (14 mL), TBAF (1 *M* in THF, 270 μL, 0.27 mmol) was added under an Ar atmosphere. After stirring for 3 h at 25 °C, workup and purification by flash chromatography on silica gel (hexane/EtOAc, 95:5) afforded **4c** (47 mg, 83%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.62 (dd, *J* = 2.1, 0.8 Hz, 1 H), 7.67 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.38 (dd, *J* = 8.1, 0.8 Hz, 1 H), 3.02 (s, 1 H), 3.04 (s, 1 H), 1.22 (s, 9 H, *t*Bu), 1.21 (s, 9 H, *t*Bu), 1.18 (s, 9 H, *t*Bu), 1.17 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 212.9 (C, C=*C*=C), 212.4 (C, C=*C*=C), 152.2 (CH), 142.0 (C), 138.4 (CH), 126.6 (CH), 119.7 (C), 103.5 (C), 103.3 (C), 103.1 (C), 103.0 (C), 92.0 (C), 89.4 (C), 85.5 (C), 81.2 (CH, -C≡*C*-H), 81.1 (CH, -C≡*C*-H), 35.9 (C, *t*Bu), 35.8 (C, *t*Bu), 35.5 (C, *t*Bu), 35.5 (C, *t*Bu), 29.2 (3×CH_3, *t*Bu), 29.1 (3×CH_3, *t*Bu), 29.0 (3×CH_3, *t*Bu), 28.9 (3×CH_3, *t*Bu) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{42}N^+$ 476.33118; found 476.33158.

5,5′-(3,5,10,12-Tetra-*tert*-butyltetradeca-3,4,10,11-tetraen-1,6,8,13-tetrayne-1,14-diyl)bis[2-(3,5-di-*tert*-butylhepta-3,4-dien-1,6-diyn-1-yl)pyridine] (5c): Monodeprotected heterotrimer **16c**[4d] (1.33 g, 2.10 mmol) was dissolved in toluene (100.0 mL). To this solution, [$PdCl_2(PPh_3)_2$] (0.10 g, 0.15 mmol), CuI (29 mg, 0.15 mmol) and TMEDA (480 μL, 3.10 mmol) were added, and the mixture was stirred and heated to reflux (110 °C) under an air atmosphere for 28 h. The reaction mixture was then partitioned between saturated aqueous NH_4Cl solution and dichloromethane. The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude material obtained was redissolved in THF (80 mL), TBAF was added (1 M in THF, 2.6 mL, 2.6 mmol), and the reaction mixture was stirred at 25 °C under an argon atmosphere. After 1 h, the solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous $NaHCO_3$ solution and dichloromethane. The aqueous phase was extracted with dichloromethane, the combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by FC on silica gel (hexane/CH_2Cl_2, 1:1) afforded **5c** (740 mg, 71%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.61 (d, *J* = 1.6 Hz, 2 H), 7.66 (dd, *J* = 8.1, 1.6 Hz, 2 H), 7.37 (d, *J* = 8.1 Hz, 2 H), 3.04 (s, 2 H), 1.22 (s, 18 H), 1.20 (s, 18 H), 1.17 (s, 36 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 214.3 (2 C, C=*C*=C), 212.2 (2 C, C=*C*=C), 152.1 (2×CH), 141.9 (2×C), 138.1 (2×CH), 126.4 (2×CH), 119.5 (2×C), 103.7 (2×C), 103.6 (2×C), 103.4 (2×C), 102.8 (2×C), 92.3 (2×C), 89.3 (2×C), 87.9 (2×C), 84.5 (2×C), 80.9 (2×C), 77.6 (2×C), 77.1 (2×C), 75.1 (2×C), 36.0 (2×C, *t*Bu), 35.9 (2×C, *t*Bu), 35.6 (2×C, *t*Bu), 35.3 (2×C, *t*Bu), 29.05 (6×CH_3, *t*Bu), 29.00 (12×CH_3, *t*Bu), 28.8 (6×CH_3, *t*Bu) ppm. HRMS (ESI): calcd for $C_{70}H_{81}N_2^+$ [M + H]$^+$ 949.6394; found 949.6362.

Intermolecular Approach

4,6,11,13,19,21,26,28-Octa-*tert*-butyl-1,16(9,10)dianthracenacyclotriacontaphane-4,5,11,12,19,20,26,27-octaen-2,7,9,10,14,17,22,24,29-octayne (3a)

Hay Coupling Reaction: A round-bottom flask was flame-dried under a flow of dry argon. To the flask, CuI (35 mg, 0.18 mmol), TMEDA (54 mg, 0.46 mmol), and dichloroethane (5 mL) were added. Oxygen was bubbled into the solution for 1 h at ambient temperature to afford the Hay catalyst. In the second round-bottom flask, a solution of **4a** (14 mg, 0.024 mmol) in dichloroethane

(9 mL) was prepared. The solution was stirred at ambient temperature while oxygen was bubbled from an inlet tube. The solution of **4a** was added dropwise by using a syringe pump to the Hay catalyst over a period of 29 h. After stirring the reaction for an additional 92 h, the dichloromethane was evaporated under reduced pressure and the residue was washed with KCN. The aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/CH_2Cl_2, 4:1) gave diiodinated **11a** (17 mg, 85%) and traces of **12a**.

Pd/Cu Method: Two solutions were prepared: (1) A solution of $[PdCl_2(PPh_3)_2]$ (2.8 mg, 4 μmol), CuI (1.6 mg, 8.4 μmol), and TMEDA (77 mg, 0.66 mmol) in toluene (4.5 mL); (2) A solution of **4a** (19 mg, 0.033 mmol) in toluene (12 mL). Both solutions were bubbled with oxygen for 1 h at ambient temperature. Solution 1 was heated at 60 °C, then Solution 2 was added dropwise by using a syringe pump over a period of 30 h. After stirring the reaction for an additional 18 h, the toluene was evaporated and the residue was washed with NH_4Cl. The aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/CH_2Cl_2, 4:1) gave **3a** (12 mg, 63%) along with **13a** (5 mg, 26%).

Breslow Method: CuCl (156 mg, 1.57 mmol) and $CuCl_2$ (31 mg, 0.23 mmol) were dissolved in anhydrous pyridine (12 mL), and the solution was degassed by bubbling Ar for 60 min. A solution of **4a** (12 mg, 0.021 mmol) in anhydrous pyridine (8.4 mL) was added over a period of 25 h. After 115 h, the solvent was removed under reduced pressure; the remaining solid was dissolved in CH_2Cl_2 and washed with saturated aqueous KCN solution. The aqueous phase was extracted with CH_2Cl_2, dried with Na_2SO_4, and the solvents were evaporated to dryness. The obtained solid was purified by flash chromatography (SiO_2; hexane/CH_2Cl_2, 4:1) to give **3a** (7 mg, 58%) along with **13a** (2 mg, 17%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.46–8.36 (m, 8 H), 7.53–7.44 (m, 8 H), 1.41–1.32 (m, 36 H, *t*Bu), 1.31–1.25 (m, 36 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 215.0–214.6 (C=*C*=C), 131.9–131.7 (overlapped signals), 127.1–126.7 (overlapped), 126.6–126.4 (overlapped), 118.6–118.2 (overlapped), 105.6–104.8 (overlapped), 103.4–103.2 (overlapped), 96.1–95.4 (overlapped), 90.9–90.3 (overlapped), 77.7–77.1 (overlapped), 75.6–75.2 (overlapped), 36.4–35.2 (overlapped), 29.6–29.1 (overlapped) ppm. MALDI-MS: *m*/*z* = 1145 (41) $[M^+]$, 1088 (93) $[M - Me_3C]^+$. HRMS (MALDI): calcd. for $C_{88}H_{88}^+$ $[M]^+$ 1144.6886; found 1144.6870. IR (neat): $\tilde{\nu}$ = 2962, 1737, 1474, 1459, 1392, 1361, 1222, 1125, 1077, 1025, 906, 764, 639 cm^{-1}. UV/Vis (hexane): λ_{max} (ε, L mol^{-1} cm^{-1}) = 213 (133200), 233 (97900), 273 (200300), 303 (70600), 433 (61200), 459 (59300) nm.

9,10-Bis(3,5-di-*tert*-butyl-7-iodohepta-3,4-dien-1,6-diyn-1-yl)anthracene (11a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.57–8.49 (m, 1 H), 7.68–7.56 (m, 1 H), 1.39 (s, 9 H), 1.27 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 213.74 (C=*C*=C), 132.2 (C), 27.3 (CH), 126.9 (CH), 118.8 (C), 105.0 (C), 104.3 (C), 96.3 (C), 90.2 (C), 87.41 (C), 36.2 (C, *t*Bu), 36.1 (C, *t*Bu), 29.5 (CH_3, *t*Bu), 29.21 (CH_3, *t*Bu) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{44}H_{44}I_2^+$ 827.15981; found 827.16051.

Data for 13a: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.55–8.44 (m, 12 H), 7.59–7.53 (m, 12 H), 1.37 (s, 27 H), 1.36 (s, 27 H), 1.27 (s, 54 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.7–214.2 (m, C=*C*=C), 132.1–131.9 (m), 127.1, 126.7, 118.6, 105.2–104.9, 103.3–103.1, 95.8–95.4, 90.6–90.3, 77.7–77.1, 75.3, 36.4–35.7, 29.3, 29.2 ppm. MALDI-MS: *m*/*z* (%) = 1741 (5) $[M + Na]^+$, 1661 (30) $[M - Me_3C]^+$. $C_{132}H_{132}$ (1718.5): C 92.26, H 7.74; found C 92.24, H 7.75. UV/Vis (hexane): λ_{max} (ε, L mol^{-1} cm^{-1}) = 213 (89300), 233 (86300), 273 (154000), 303 (57500), 433 (49200), 459 (50700) nm.

4,6,11,13,19,21,26,28-Octa-*tert*-butyl-1,16(2,5)dipyridinecyclotriacontaphane-4,5,11,12,19,20,26,27-octaen-2,7,9,10,14,17,22,24,29-octayne (3c)

Hay Coupling Reaction: A round-bottom flask was flame-dried under a flow of dry argon. To the flask, CuI (83 mg, 0.43 mmol), TMEDA (132 mg, 1.13 mmol) and dichloroethane (10 mL) were added. Oxygen was bubbled into the solution for 1 h at ambient temperature to afford the Hay catalyst. In the second round-bottom flask a solution of **4c** (24 mg, 0.05 mmol) in dichloroethane (22 mL) was prepared. The solution was stirred at ambient temperature while oxygen was bubbled from an inlet tube. The solution of **4c** was added dropwise by using a syringe pump to the Hay catalyst over a period of 40 h. After stirring the reaction for an additional 105 h, the dichloromethane was evaporated under reduced pressure and the residue was washed with KCN. The aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/CH_2Cl_2, 70:30) afforded the diiodo compounds **11c** (26 mg, 71%) and **12c** (identified by mass spectroscopy) along with traces of pyrido-alleno-acetylenic cyclophane **3c**.

Pd/Cu Method: Two solutions were prepared: (1) A solution of $[PdCl_2(PPh_3)_2]$ (1.5 mg, 2.1 μmol), CuI (1 mg, 5.2 μmol), and TMEDA (37 mg, 0.32 mmol) in toluene (2 mL). (2) A solution of **4c** (6 mg, 0.012 mmol) in toluene (6 mL). Both solutions were bubbled with oxygen for 1 h at ambient temperature. Solution 1 was heated at 60 °C, then Solution 2 was added dropwise by using a syringe pump over a period of 23 h. After stirring the reaction for an additional 72 h, the toluene was evaporated and the residue was washed with KCN. The aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (hexane/CH_2Cl_2, 70:30) gave **3c** (3.5 mg, 56%).

Breslow Method: CuCl (172 mg, 1.73 mmol) and $CuCl_2$ (34 mg, 0.25 mmol) were dissolved in anhydrous pyridine (13 mL), and the solution was degassed by bubbling Ar for 60 min. A solution of **4c** (11 mg, 0.023 mmol) in anhydrous pyridine (8.5 mL) was added over a period of 21 h. After 89 h, the solvent was removed under reduced pressure and the remaining solid was dissolved in CH_2Cl_2 and washed with a saturated aqueous EDTA solution. The aqueous phase was extracted with CH_2Cl_2, dried with Na_2SO_4, and the solvents were evaporated to dryness. The obtained solid was purified by flash chromatography (SiO_2; hexane/CH_2Cl_2, 70:30) to give **3c** (6 mg, 54%) as a white solid.

2,5-Bis[3,5-di(*tert*-butyl)-7-iodohepta-3,4-diene-1,6-diyn-1-yl]pyridine (11c): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.61 (dd, *J* = 2.1, 0.8 Hz, 1 H), 7.67 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.38 (dd, *J* = 8.1, 0.8 Hz, 1 H), 1.21 (s, 9 H), 1.20 (s, 9 H), 1.16 (s, 9 H), 1.15 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 213.9 (C, C=*C*=C), 213.4 (C, C=*C*=C), 152.2 (CH), 141.9 (C), 138.4 (CH), 126.6 (CH), 119.7 (C), 104.7 (C), 104.6 (C), 103.8 (C), 103.5 (C), 92.0 (C), 91.9 (C), 89.4 (C), 88.4 (C), 87.1 (C), 87.1 (C), 36.0 (C, *t*Bu), 36.0 (C, *t*Bu), 36.0 (C, *t*Bu), 29.2 (3 × CH_3, *t*Bu), 29.1 (3 × CH_3, *t*Bu), 29.0 (3 × CH_3, *t*Bu), 29.0 (3 × CH_3, *t*Bu) ppm. HRMS (ESI): calcd. for $C_{35}H_{40}I_2N^+$ 728.1244; found 728.12684.

Intramolecular Approach

4,6,11,13,19,21,26,28-Octa-*tert*-butyl-1,16(2,5)dipyridinecyclotriacontaphane-4,5,11,12,19,20,26,27-octaen-2,7,9,10,14,17,22,24,29-octayne (3c): Compound **5c** (36 mg, 0.04 mmol) was dissolved in O_2-free pyridine (20.0 mL) and treated with anhydrous CuCl (620 mg, 6.08 mmol) and anhydrous $CuCl_2$ (91 mg, 0.61 mmol) for 1 h at 25 °C. The solvent was then removed under reduced pressure and the residue was partitioned between saturated aqueous EDTA (sat) and EtOAc. The aqueous phase was extracted with EtOAc, the combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by FC on silica gel (hexane/CH_2Cl_2, 1:1) gave **3c** (27 mg, 75%) as a solid.

Pyrido-alleno-acetylenic cyclophanes **3c** was obtained as a mixture of six diastereoisomers, which could be isolated by HPLC (peaks A–F) on the stationary phase Rexchrom "Buckyclutcher 1" [preparative; 10 μm 100 Å Trident-TriDNP; 50 cm × 21.1 mm ID; hexane/CH_2Cl_2, 22%; 10 mL/min; λ = 320 nm) (see Figure SI.1 in the Supporting Information).

Data for 3c-A: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.60–8.56 (m, 2 H), 7.67–7.65 (m, 2 H), 7.39–7.37 (m, 2 H), 1.21 (s, 18 H), 1.19 (s, 18 H), 1.173 (s, 18 H), 1.167 (s, 18 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 215.0 (2 × C, C=*C*=C), 214.7 (2 × C, C=*C*=C), 151.9 (2 ×CH), 142.0 (2 C), 138.3 (2 × CH), 126.7 (2 × CH), 119.4 (2 × C), 103.9 (C), 103.7 (C), 103.6 (C), 103.5 (C), 92.3 (4 × C), 89.8 (4 × C), 87.5 (4 × C), 84.6 (4 × C), 75.5 (2 × C), 75.3 (2 × C), 35.69–35.61 (m, 8 × C, *t*Bu), 29.1–29.0 (m, 24 × CH_3, *t*Bu) ppm. HRMS (ESI): calcd. for $C_{70}H_{79}N^{2+}$ [M + 2H]$^+$ 947.6238; found 947.6236.

Data for *twist*-3c-B: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.60–8.57 (m, 2 H), 7.67–7.64 (m, 2 H), 7.41–7.35 (m, 2 H), 1.22 (s, 18 H, *t*Bu), 1.20–1.16 (m, 54 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 215.2, 215.0, 214.5, 214.5, 151.9, 151.9, 142.0, 138.4, 138.3, 138.3, 138.2, 126.6, 119.4, 119.3, 104.0, 103.8, 103.8, 103.7, 103.6, 103.5, 92.5, 92.3, 89.9, 89.8, 87.7, 87.6, 84.8, 84.7, 35.6, 29.7, 29.1, 29.0 ppm. HRMS ESI: calcd. for $C_{70}H_{79}N^{2+}$ [M + 2H]$^+$ 947.6238; found 947.6251.

Data for *twist*-3c-D: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.59–8.57 (m, 2 H), 7.66–7.62 (m, 2 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 1.17 (s, 9 H), 1.18 (s, 9 H), 1.20 (s, 9 H), 1.20 (s, 9 H), 1.20 (s, 9 H), 1.20 (s, 27 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 214.9, 214.9, 214.8, 214.7, 151.8, 141.9, 141.9, 138.3, 138.2, 126.7, 126.6, 119.4, 119.3, 103.9, 103.7, 103.7, 103.7, 103.7, 103.6, 103.5, 92.4, 92.3, 89.9, 89.8, 87.7, 87.6, 84.9, 84.8, 35.6, 35.6, 35.5, 29.0, 28.8 ppm. HRMS (ESI): calcd. for $C_{70}H_{79}N_2^+$ [M + 2H]$^+$ 947.6238; found 947.6224.

Supporting Information (see footnote on the first page of this article): Preparation of **6**; copies of ^{1}H and ^{13}C NMR spectra for all products; AM1 geometries of *twist*-**3a** and *twist*-**3b** are included together with the AM1 geometries for all diastereoisomers of **3c**.

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[14] The introduction of an anthracene ring confers fluorescence to the final macrocycle. In fact, **1a** emits at 478–481 and 510–515 nm when a hexane solution was excited (λ_{ex} = 315 nm) at 25 °C with remarkable fluorescence quantum yield (*f* = 0.2); see ref.[4a]

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