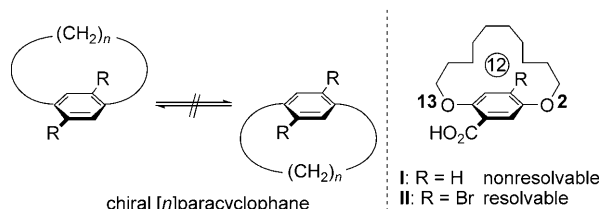


Hydrogen-Bond Control in Axially Chiral Styrenes: Selective Synthesis of Enantiomerically Pure C_2 -Symmetric Paracyclophanes**

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Planar-chiral cyclophanes are of interest not only from a structural point of view, but also in terms of their potential utility in materials science^[1] and asymmetric catalysis.^[2] So far, however, the potential of such structures has not been exploited to any great extent owing to two major hurdles.

The first issue is how to secure stable planar chirality. To avoid flipping of the ansa chain, and hence racemization, two general strategies are available: 1) the use of a shorter ansa chain,^[3] and 2) the installment of many and/or large substituents on the aromatic ring. Scheme 1 illustrates the narrow borderline between resolvable and nonresolvable structures: The [12]cyclophane **II** with two substituents is resolvable, whereas **I** with a single substituent is not resolvable.^[4]



Scheme 1. Stereochemical features of paracyclophanes.

Even when such guidelines are followed, another challenge is the enantioselective synthesis of these structures;^[5,6] tedious optical resolution has been the approach traditionally employed.^[7] Herein, we propose a fairly general strategy for the synthesis of enantiomerically pure cyclophanes.

The strategic basis for our approach is a symmetry consideration illustrated by a “plate-and-stick model” (Figure 1): The connection of two identical sticks to the upper side of a C_{2h} -symmetric plate **A**, which represents an aromatic platform, would give the C_2 -symmetric “precyclophane” **B**. To complete an enantioselective route to the C_2 -

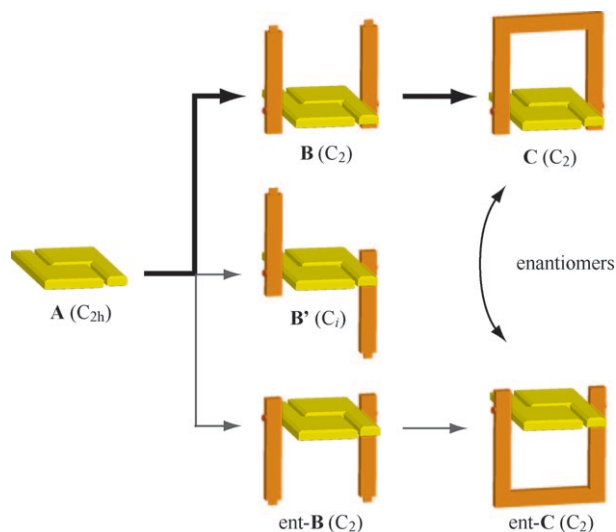
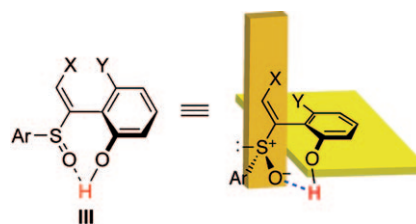


Figure 1. Plate-and-stick model for the construction of C_2 -symmetric cyclophane architectures.

symmetric cyclophane **C**, the two sticks need to be connected to one another.

We envisaged that an axially chiral styrene **III** (Scheme 2) would be an ideal precursor for the juxtaposition of two sticks on the same side of the plane as in **B** in preparation for ansa bridging. As recently demonstrated in natural product synthesis, a hydrogen bond between the sulfinyl oxygen atom and the phenol hydroxy group is able to control the local conformation of the styrene motif (Scheme 2).^[8]

Scheme 3 shows our planned approach: When two vinyl sulfoxide moieties with the same configuration are installed at the 2- and 5-positions of a *p*-hydroquinone, as in **IV**, two hydrogen bonds cooperate to line up the two side chains for ansa-chain formation. The C_2 symmetry also facilitates the synthesis of the key compound **IV**, which can be assembled from an aryl diboronic acid **V** and two equivalents of vinyl iodide **VI**.^[7]



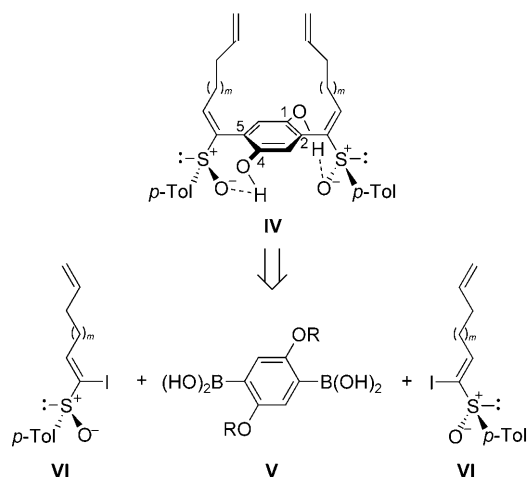
Scheme 2. Conformational control of axially chiral styrenes by hydrogen bonding.

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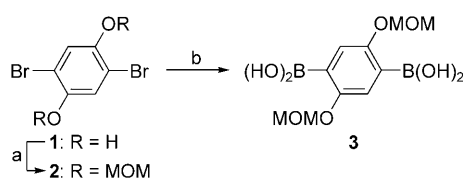
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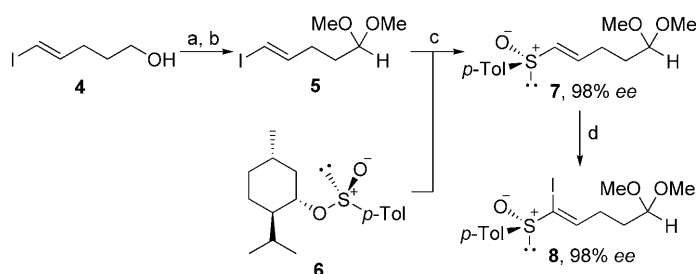
Scheme 3. Retrosynthesis of the cyclization precursor.

The first coupling partner, aryl diboronate **3**, was obtained in two steps from hydroquinone **1**^[9] by protection of the two hydroxy groups as MOM ethers, followed by treatment with *n*BuLi and (*i*PrO)₃B and acidic workup (Scheme 4).



Scheme 4. Synthesis of **3**: a) MOMCl, *i*Pr₂NEt, CH₂Cl₂, room temperature, 8 h, 96%; b) *n*BuLi, THF, −78 °C, 30 min; (*i*PrO)₃B, −78 → 0 °C, 2 h; 2 M HCl, 0 °C, 30 min, 84%. MOM = methoxymethyl.

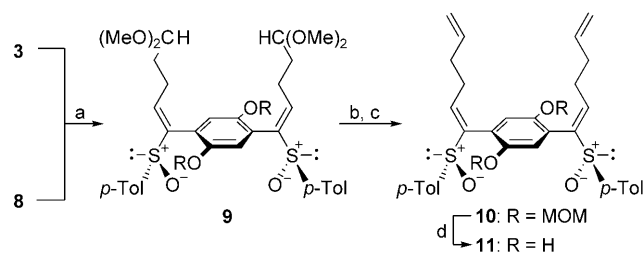
Vinyl iodide **8** was prepared from alcohol **4**:^[10] Swern oxidation of **4**, followed by acetalization, afforded iodide **5** in 80 % yield (Scheme 5). Treatment of the vinyl lithium species generated from **5** (*t*BuLi, Et₂O, −78 °C) with the Andersen reagent (*R*)-**6**^[11] and subsequent iodination gave vinyl iodide **8** with 98 % *ee*, as determined by HPLC on a chiral stationary



Scheme 5. Synthesis of **8**: a) (COCl)₂, DMSO, Et₃N, −78 °C → RT, 2 h, 83%; b) Bu₄NBr₃, HC(OMe)₃, MeOH, room temperature, 11 h, 96%; c) *t*BuLi, Et₂O, −78 °C, 1 h; **6** (1.0 equiv), −78 °C, 10 min, 87%; d) LDA, THF, −78 °C, 15 min; I₂, THF, −78 → −45 °C, 1 h, 76%. DMSO = dimethylsulfoxide, LDA = lithium diisopropylamide.

phase (Daicel chiralpak AS, ϕ 0.46 cm × 25 cm, *n*-hexane/*i*PrOH 2:1).

The cyclization precursor **11** was assembled from diboronate acid **3** and two equivalents of the chiral vinyl iodide **8** (Scheme 6). Although the product **9** of the coupling reaction



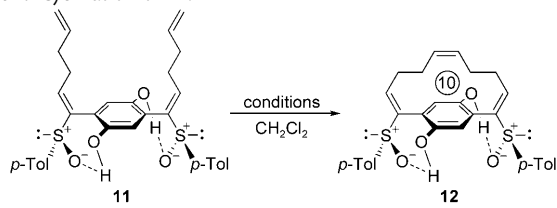
Scheme 6. Synthesis of **11**: a) **3** (1.0 equiv), **8** (2.3 equiv), [Pd(PPh₃)₄] (30 mol %), K₃PO₄, 1,2-dimethoxyethane, H₂O, 85 °C, 4 h; b) TsOH·H₂O, acetone, H₂O, 60 °C, 2 h; c) Ph₃PCH₂Br, *n*BuLi, THF, 0 °C, 10 min, 74 % (3 steps); d) SnBr₂, toluene, 65 °C, 3.5 h, 85 %. Ts = *p*-toluenesulfonyl.

was accompanied by impurities derived from the palladium catalyst, hydrolysis of the acetal functionalities, followed by a Wittig reaction, enabled facile isolation of the pure bisulfonate **10** (74 % yield from **3**). Removal of the two MOM groups in **10** gave hydroquinone **11** in 85 % yield. The ¹H NMR spectrum of **11** suggested promising implications for the projected formation of the ansa chain: A C₂-symmetric conformation was indicated by the simple spectral pattern, and the presence of two equivalent hydrogen bonds was indicated by the low-field resonance of the phenol protons (δ = 8.9, singlet, 2H).

Our initial attempt at the cyclization of **11**, by treatment with the first-generation Grubbs catalyst **A**^[12] (CH₂Cl₂ (0.01 M)), afforded the [10]paracyclophane **12** in 2 % yield (Table 1, entry 1). The low yield seemed ascribable to the formation of polymeric products through competing intermolecular reactions. To suppress the polymerization, the reaction was conducted at a lower concentration (0.001 M). Under these conditions, **12** was obtained in 21 % yield (Table 1, entry 2). Furthermore, when the reaction was carried out at 40 °C, the yield was improved to 50 % (Table 1, entry 3).

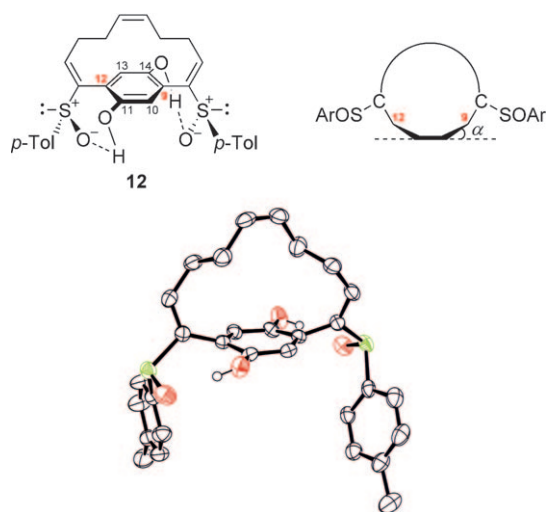
Other carbene catalysts were not effective; however, the case of the second-generation Grubbs catalyst **B**^[13] is interesting (Table 1, entry 4): Although the starting material **11** was consumed smoothly, only polymeric products were formed. We concluded that cyclophane **12**, once formed, underwent ring-opening polymerization in situ and that the newly formed C=C bond in **12** is reactive as a result of its strained nature (see below).

The stereochemical integrity of cyclophane **12** is notable. This macrocycle was formed in diastereomerically (¹H NMR) and enantiomerically pure form (with > 99 % *ee*, as determined by HPLC on a chiral phase (Daicel chiralpak IA, ϕ 0.46 cm × 25 cm, *n*-hexane/*i*PrOH 2:1)).^[14] Furthermore, single-crystal X-ray analysis of **12** (Figure 2) revealed several interesting structural features: 1) the *Z* configuration of the newly formed double bond,

Table 1: Cyclization of **11**.^[a]


Entry	Catalyst	Concentration of 11 [M]	T [°C]	t [h]	Yield [%]	
					12	11
1	A	0.01	RT	41	2	8
2	A	0.001	RT	42	21	—
3	A	0.001	40	18	50	9
4	B	0.001	40	10	—	trace

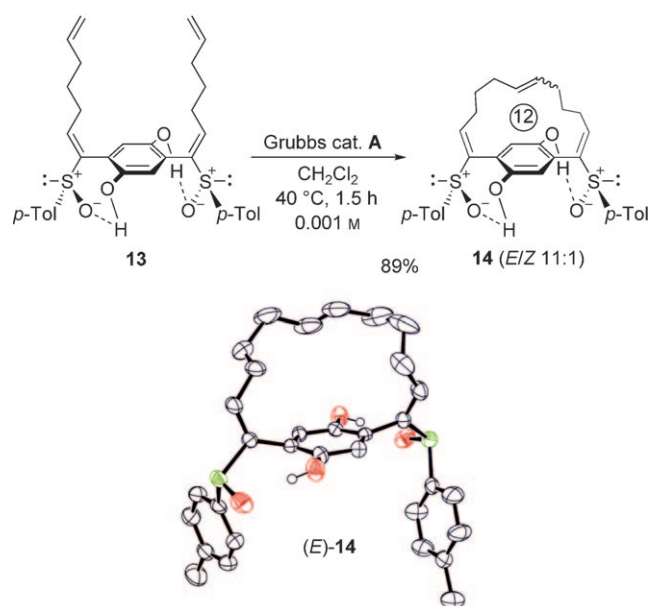
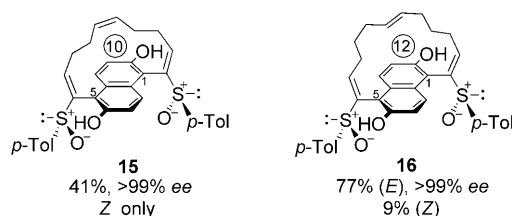
[a] All reactions were carried out with 30 mol% of the catalyst in degassed CH₂Cl₂.

**Figure 2.** X-ray crystal structure of **12**. Hydrogen atoms (except those of the phenol hydroxy groups) are omitted for clarity.

and 2) the bent benzene ring, in which the C9 and C12 carbon atoms deviate from the C10–C11–C13–C14 plane at an angle of approximately 7° (6.9 and 7.2°).^[15] Such a distortion would naturally make the molecule more reactive. Indeed, as a mentioned above, cyclophane **12** was consumed quickly by ring-opening polymerization upon treatment with the Grubbs catalyst **B** (0.5 h, 40 °C).

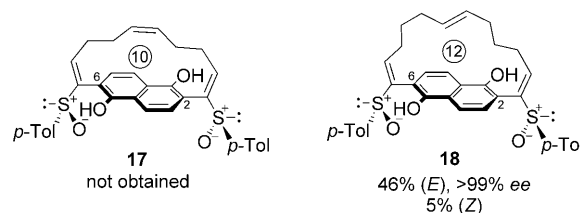
Tetraene **13**,^[16] in which the side chains are one-carbon-atom longer than those in **11**, underwent smooth cyclization in 1.5 h under the optimal conditions found for the cyclization of **11**, to give the [12]paracyclophane **14** in excellent yield (Figure 3). The facile cyclization reflects the favorable spatial relationship of the two terminal double bonds in **13**, and the less strained nature of the cyclized product **14**. Two separable geometrical isomers were obtained, whereby the *E* isomer prevailed (*E/Z* 11:1). Single-crystal X-ray analysis of (*E*)-**14** showed the smaller distortion angles of the benzene ring (4.8 and 6.5°).^[15]

We also synthesized the related cyclophanes **15** and **16**, with a 1,5-naphthalene core. Again, the length of the ansa

**Figure 3.** Synthesis and X-ray crystal structure of (*E*)-**14**. Hydrogen atoms (except those of the phenol hydroxy groups) are omitted from the X-ray crystal structure for clarity.

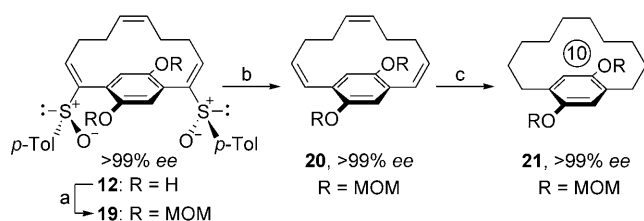
chain affected the cyclization yields and *E/Z* selectivity: The [10]paracyclophane **15** was obtained in only moderate yield (41%), and the geometry of the resulting olefin was exclusively *Z*; by contrast, the [12]paracyclophane **16** was obtained in high yield (86 %) with high *E* selectivity.

Such a chain-length dependence was also pronounced for the 2,6-naphthalene congeners. Cyclization to form the [10]paracyclophane **17** was not possible: Only polymeric



products were obtained, presumably owing to the unfavorable distance between two terminal olefins and the high strain expected upon cyclization. By contrast, cyclization to form the corresponding [12]paracyclophane **18** proved possible, albeit in moderate yield. The *E* isomer was obtained as the major product.^[17]

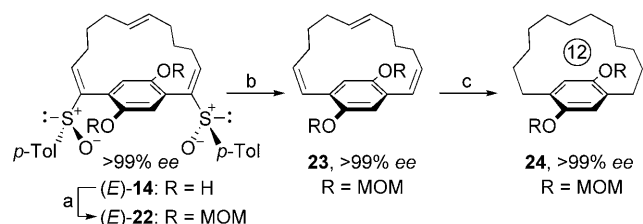
The bisulfanyl cyclophane **12** was desulfurized and converted into the saturated congener **21** (Scheme 7): The



Scheme 7. Synthesis of **21**: a) MOMCl, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , 40°C , 5 h, 93%; b) $t\text{BuLi}$, toluene, -78°C , 5 min, 70%; c) H_2 , 10% Pd/C, MeOH, room temperature, 1 h, quantitative.

two phenol hydroxy groups in **12** were masked as MOM ethers to give **19**, and the sulfinyl groups were removed by treatment with $t\text{BuLi}$. Quenching with MeOH then gave triene **20**.^[14] We had been concerned that racemization might occur upon the removal of the two sulfinyl groups; however, the planar chirality was maintained, and **20** was obtained in enantiomerically pure form. Furthermore, hydrogenation of **20** (H_2 , Pd/C, MeOH) gave the saturated cyclophane **21** in enantiomerically pure form (with $>99\%$ ee, as determined by HPLC on a chiral phase (Daicel chiralpak IB, ϕ 0.46 cm $\times$ 25 cm, hexane/ $i\text{PrOH}$ 99:1)).^[14]

The same sequence of transformations enabled the conversion of (*E*)-**14**, via triene **23**, into [12]paracyclophane **24** (Scheme 8). Although the [12]paracyclophanes are configurationally less stable than the [10]paracyclophane analogues, **24** was obtained without any loss of planar chirality ($>99\%$ ee).^[14]



Scheme 8. Synthesis of **24**: a) MOMCl, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , 40°C , 5 h, 92%; b) $t\text{BuLi}$, toluene, -78°C , 5 min, 75%; c) H_2 , 10% Pd/C, MeOH, room temperature, 1 h, quantitative.

To investigate the thermal stability of the planar chirality, [10]paracyclophanes **20** and **21** and [12]paracyclophanes **23** and **24** were heated in refluxing toluene. In all cases, no appreciable racemization was observed. Notably, even in the configurationally metastable [12]paracyclophane derivatives **23** and **24**, the planar chirality was maintained completely (12 h).

In summary, we have developed a new approach for the preparation of enantiomerically pure planar-chiral [10]- and [12]paracyclophanes, which will serve as versatile intermediates for the synthesis of various other cyclophane derivatives.

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- [15] CCDC 727141 (**12**) and 727142 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [16] For the preparation of tetraene **13**, see the Supporting Information.
- [17] These naphthalenophanes showed an interesting anisotropic shift in the ^1H NMR spectra. The signals of the protons attached to the newly formed C=C bond appeared at higher fields in comparison with those of the benzene analogues (**12**: $\delta = 5.26$, **15**: $\delta = 4.97$). This tendency could be attributed to the stronger anisotropic effect of a naphthalene system relative to that of a benzene ring and/or to the closer spatial relationship of the vinyl hydrogen atoms to the π -electron cloud in the naphthalene system; see: a) T. Kusumi, H. Takahashi, T. Hashimoto, Y. Kan, Y. Asamawa, *Chem. Lett.* **1994**, 1093–1094; b) T. Kusumi, H. Takahashi, P. Xu, T. Fukushima, Y. Asakawa, T. Hashimoto, Y. Kan, Y. Inoue, *Tetrahedron Lett.* **1994**, *35*, 4397–4400.