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Stereospecific ring expansion from orthocyclophanes with central chirality to metacyclophanes with planar chirality

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Carbon-carbon bonds constitute the major framework of organic molecules and carbon-hydrogen bonds are abundant in their peripheries. Such nonpolar σ -bonds are thermodynamically stable and kinetically inert in general. Nonetheless, selective activation of those ubiquitous bonds may offer a straightforward method to construct and/or functionalize organic skeletons. Herein we describe ring expansion from orthocyclophanes to metacyclophanes occurring upon sequential action of light and a metal catalyst. Formally, specific non-strained carbon-hydrogen and carbon-carbon bonds are cleaved and exchanged without elimination of any leaving groups. Notably, the product is energetically uphill from the starting material, but the endergonic photocyclization step makes it possible to drive the transformation forward. The ring expansion is extended to the stereospecific synthesis of metacyclophanes possessing planar chirality, during which central chirality on a tertiary carbon is transferred to planar chirality.

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The number of functional groups that can be transformed by transition metal catalysis has been considerably expanded. Carbon-carbon (C-C)^{1–15} and carbon-hydrogen (C-H) bonds^{16–25}, which are ubiquitous in organic compounds, are intrinsically difficult to activate owing to their thermodynamic stability as well as their kinetic inertness. Selective transformation of such nonpolar σ -bonds has provided a challenge that has motivated and inspired chemists to seek ways to activate these bonds over the past two decades.

Metacyclophanes are cyclic compounds that have a central arene unit with its 1,3-positions connected through an ansa chain²⁶. The arene unit can rapidly flip in many cases, but when the flipping is hindered, metacyclophanes can gain stable planar chirality. Such an intriguing chiral metacyclophane unit is found in various natural products like galeon and vancomycin²⁷. Chiral metacyclophanes also constitute a key structural component of some pharmaceuticals^{28,29} and supramolecular host materials that accept small molecules^{30–32}. Consequently, the development of methods to stereoselectively construct chiral metacyclophane skeletons has been of growing interest^{33–38}.

We herein describe a sequential process to expand orthocyclophanes **1** into their more strained constitutional isomers, metacyclophanes **2** (Fig. 1). Specific non-polar, unstrained C-H and C-C bonds are cleaved and exchanged in a formal sense. Of note is that the whole transformation is energetically uphill (*vide infra*) and atom-economical. The overall driving force ultimately derives from light. The process can also be extended to the stereoselective synthesis of metacyclophanes **4** possessing planar chirality.

Results

Ring expansion of orthocyclophane **1a** to metacyclophane **2a**.

Initially, a THF solution of orthocyclophane **1a** (0.02 M) in a Pyrex tube was irradiated with UV light (270–350 nm) for 13 h (Fig. 2a). Photocyclization^{39–41} took place to afford benzocyclobutenol (\pm)-**5a** in 92% isolated yield. Subsequently, the benzocyclobutenol (\pm)-**5a** was treated with a catalytic amount of [Rh(OH)(cod)]₂ at 60 °C in MeOH for 5 h. The benzocyclobutene ring was opened with site-selective cleavage of the C(sp²)-C(sp³) bond^{42–45} to afford [9]metacyclophane **2a** in 72% isolated yield. The ¹H NMR of **2a** shows only one singlet peak for the benzylic protons of the ansa chain (δ 3.67 (s, 2H)), suggesting that the benzene ring flips up and down freely across the ansa chain.

A two-step mechanistic sequence for the ring expansion is shown in Fig. 2b. The first step is a photo-induced ring closing reaction (Fig. 2b, top). According to the mechanism

originally proposed by Wagner *et al.*⁴¹, the ketone **1a** is electronically excited and the excited carbonyl group acts as an oxyl radical to site-specifically abstract the benzylic hydrogen^{46,47}. The resulting 1,4-biradical species **Aa**, having an *o*-phenylene linker, spontaneously generates an isomeric mixture of the *o*-quinodimethanes (*E*)- and (*Z*)-**Ba**⁴⁸. The (*Z*)-isomer having an outward-oriented hydroxy group undergoes a 4 π -electrocyclic ring closure to form benzocyclobutenol (\pm)-**5a**. On the other hand, the (*E*)-isomer having an inward-oriented hydroxy group undergoes facile 1,5-proton shift to regenerate **1a** rather than the ring closure.

The second step is a ring-opening reaction promoted by the rhodium hydroxide complex (Fig. 2b, bottom). The hydroxy group of (\pm)-**5a** is exchanged onto the rhodium hydroxide to generate rhodium benzocyclobutenolate **Ca**, in which the benzene ring likely π -coordinates to rhodium⁴⁹. Next follows β -carbon elimination, for which the π -coordination facilitates site-selective cleavage of the C(ipso)-C(sp³) bond to furnish arylrhodium **Da**. Finally, protonation produces [9]metacyclophane **2a**.

In order to assess the thermodynamics of this sequential process, DFT calculations were performed at the B3LYP/6-31 G(d) level (Gas phase at 1 atm, 298 K) (Supplementary Fig. 1). The results suggest that (\pm)-**5a** and **2a** are thermodynamically less stable than **1a** by ca. 32.3 and 3.8 kcal mol⁻¹, respectively. The irreversible formation of highly energetic intermediate (\pm)-**5a** by the first photocyclization process makes it possible to drive the energetically uphill transformation from the reactant **1a** to its more strained constitutional isomer **2a**.

Synthesis of planar-chiral cyclophanes **4.** We next tried to utilize the arylrhodium intermediate **D** for the subsequent C-C bond formation, aiming at the synthesis of metacyclophanes having stable planar chirality. Thus, the racemic benzocyclobutenol (\pm)-**5a** was treated with a rhodium catalyst in the presence of methyl vinyl ketone (**3**, 10 equiv.) in toluene at room temperature for 10 h (Fig. 3). The reaction furnished [9]metacyclophane **4a** (69% isolated yield) that successfully incorporated **3** at the arene carbon between the 1,3-ansa chain. The ¹H NMR of **4a** shows the two distinctly coupled doublets at δ 3.44 (*d*, *J* = 14.6 Hz, 1 H) and δ 3.95 (*d*, *J* = 14.6 Hz, 1 H), indicating the inequivalency of the two benzylic protons of the ansa chain. The chiral HPLC analysis of the **4a** exhibited two peaks of equal intensities in consistence with a racemic mixture of two enantiomers. We assume that the sterics of the middle substituent prohibit the flipping of the benzene ring and give rise to stable planar chirality.

Next, our interest was directed to the stereochemical course of the ring opening/addition process, during which central chirality of benzocyclobutenol **5a** disappeared and planar chirality was generated with **4a**. The racemic mixture of benzocyclobutenol (\pm)-**5a** was successfully separated by preparative chiral HPLC to the two enantiomers (+)- and (-)-**5a**. The reaction of (+)-**5a** (>99:1 enantiomeric ratio (er)) with **3** in the presence of the achiral [Rh(OH)(cod)]₂ catalyst afforded (+)-**4a** in 72% yield (Fig. 4). A chiral HPLC analysis showed that the enantiomeric purity was retained (>99:1 er). This result assured the stereochemical integrity during the transfer of central chirality of **5a** to planar chirality of **4a** (ref. 50), letting us examine the stereospecificity of chiral transfer in more detail. Thus, the two-step ring expansion of orthocyclophane **1b** to metacyclophane (\pm)-**4b** was carried out (Fig. 5a).

The first photocyclization of **1b** afforded benzocyclobutenol (\pm)-**5b** as a single diastereomer (78% isolated yield). It was determined by NOE analysis that the hydroxy group was *trans* to the (trimethylsilyl)methyl substituent. Subsequent treatment of (\pm)-**5b** with the rhodium catalyst in the presence of **3** (10 equiv)

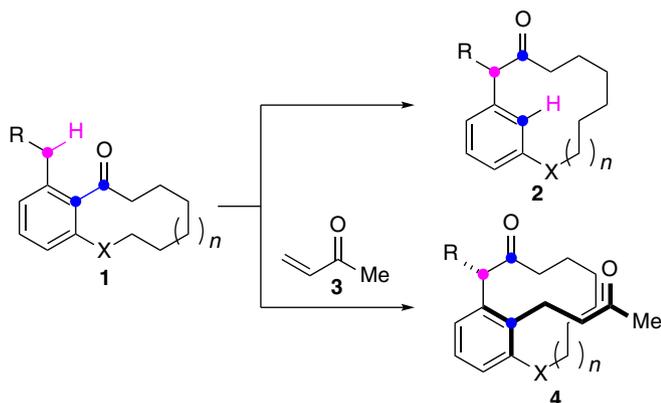


Figure 1 | Ring expansion reactions. Conversion of orthocyclophanes **1** to metacyclophanes **2** and **4**.

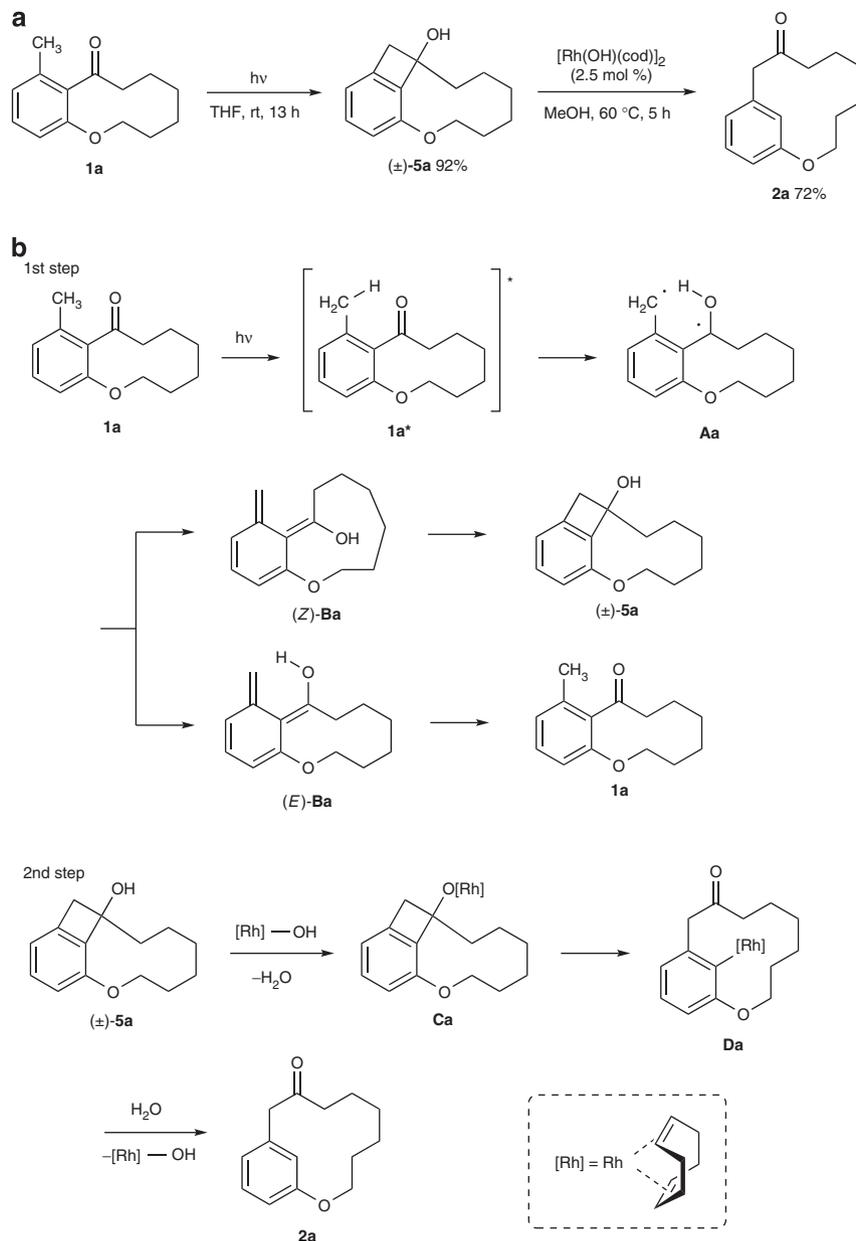


Figure 2 | Ring expansion of 1a to 2a. (a) Reaction scheme. (b) Plausible mechanism.

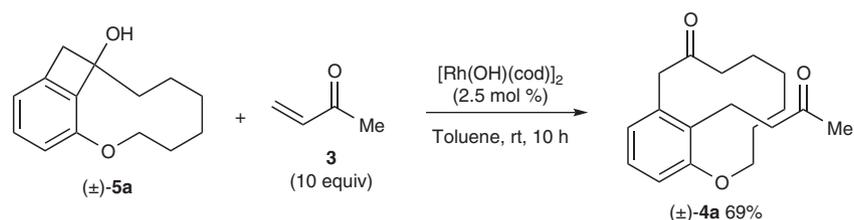


Figure 3 | Planar chiral derivatives. Rhodium-catalysed reaction of (±)-5a with 3.

in toluene at room temperature for 24 h furnished [9]metacyclophane (±)-4b in 62% isolated yield, again as a single diastereomer. No other diastereomer was detected in the crude reaction mixture. The (trimethylsilyl)methyl substituent and the C–C bond newly formed between the arene and 3 were assigned as trans to each other by a series of NMR analyses (^1H , ^{13}C , DEPT, COSY, HMQC, HMBC and NOESY).

The plausible explanation for the diastereoselectivity observed in the first photocyclization step is shown in Fig. 5b (ref. 41). Although the 1,4-biradical species **Ab** generated from **1b** potentially gives rise to four stereoisomers (*E,Z*-**Bb**, *E,E*-**Bb**, *Z,Z*-**Bb** and *Z,E*-**Bb**), the formation of (*Z,Z*-**Bb** and *Z,E*-**Bb**) is disfavoured because of steric repulsion arising between the trimethylsilylmethyl group and the ansa chain. As with the

cases of (*Z*)- and (*E*)-**Ba** in Fig. 2, the quinodimethane (*E,Z*)-**Bb** having the outward-oriented hydroxy group undergoes thermal conrotatory electrocyclic ring closure to form

trans-benzocyclobutenol (\pm)-**5b** diastereoselectively, whereas the isomer (*E,E*)-**Bb** bearing an inward-oriented hydroxy group immediately reverts to the starting ketone **1b** via facile 1,5-proton shift.

The second ring-opening step occurs with central-to-planar chirality transfer⁵⁰ (Fig. 5c). The benzene ring of the deprotonated intermediate **Cb** coordinates to rhodium to facilitate site-selective migration of the ipso *sp*² carbon onto rhodium. For the ipso carbon to migrate onto rhodium, the benzene ring flips up toward rhodium. Accordingly, the developing C–Rh linkage is *trans* to the (trimethylsilyl)methyl

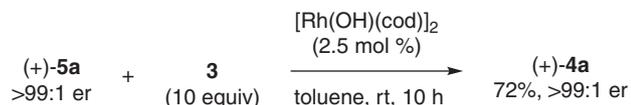


Figure 4 | Enantiopure starting materials. Synthesis of chiral cyclophane (+)-**4a**.

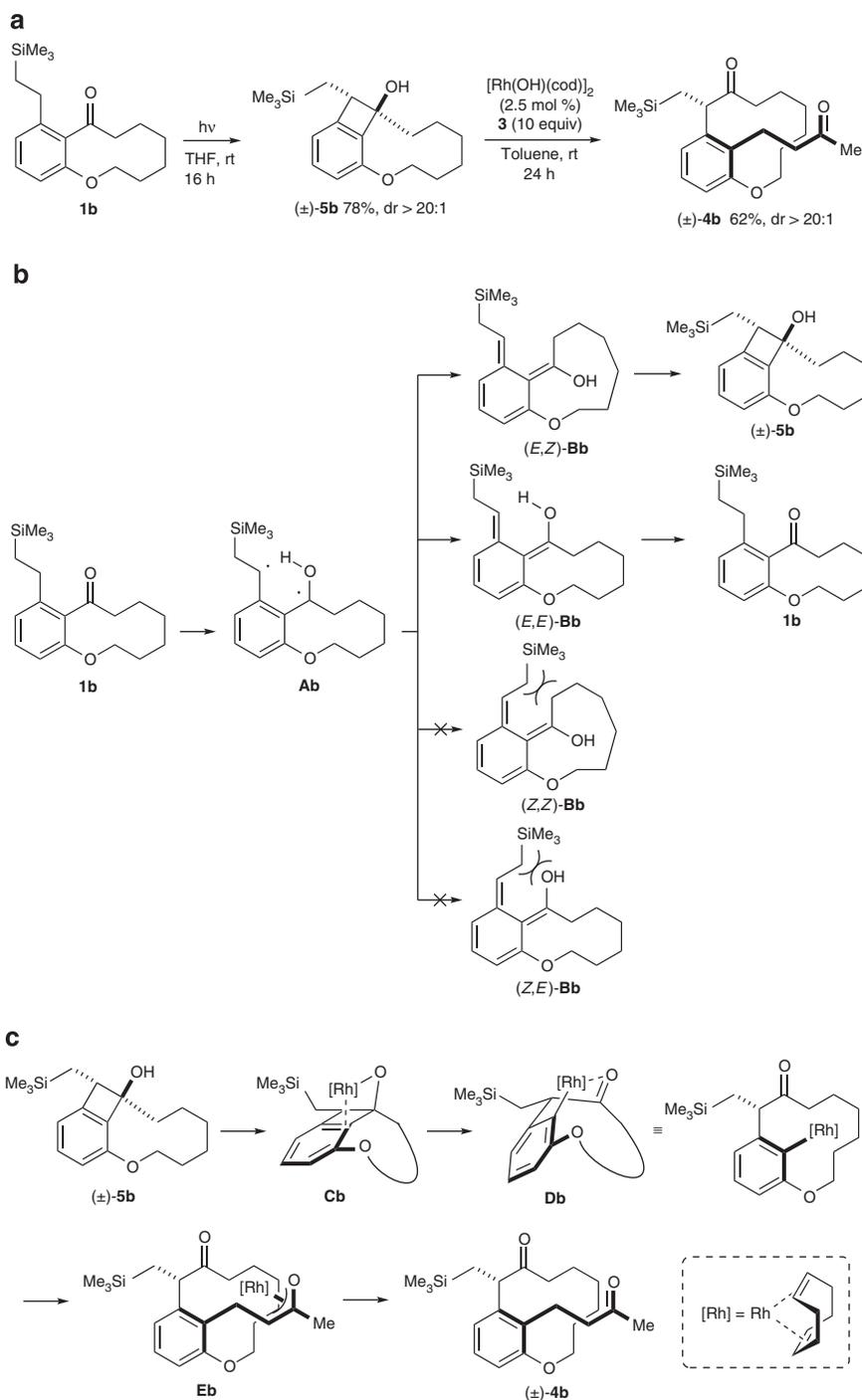


Figure 5 | Synthesis of cyclophane (\pm)-4b** from **1b**.** (a) Reaction scheme. (b) Reaction pathway from **1b** to (\pm)-**5b**. (c) Reaction pathway from (\pm)-**5b** from **4b**.

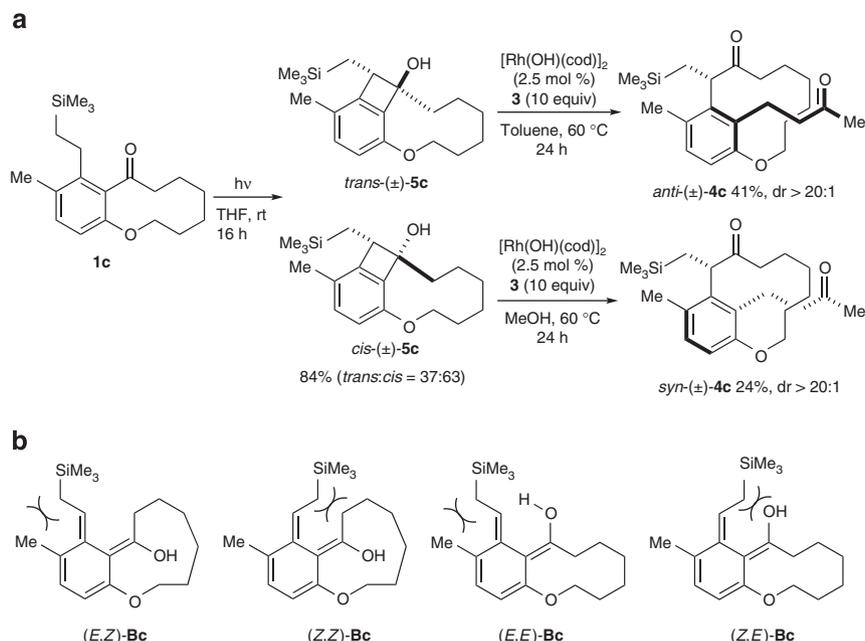


Figure 6 | Synthesis of cyclophane (\pm)-4c** from **1c**. (a) Reaction Scheme. (b) Structures of possible quinodimethane intermediates **Bc**.**

substituent with respect to the newly expanded ansa chain. The rhodium with the COD ligand on it is sterically bulky enough to prohibit the ring flipping across the ansa chain. The intermediate **Db** then undergoes conjugate addition to **3** with retention of the upward orientation of the C–Rh linkage, producing (\pm)-**4b** stereoselectively.

Stereoselective production of (\pm)-**4b** from (\pm)-**5b** provides a strong support for the validity of the stereospecificity of β -carbon elimination. Nonetheless, there remains a possibility that the formation of the diastereomer (\pm)-**4b** is favoured over that of the other diastereomer simply due to thermodynamic or kinetic reasons, rather than a mechanistic consequence. In order to examine this possibility, we next carried out the rhodium-catalysed reactions of diastereomeric benzocyclobutenols, *trans*- and *cis*-(\pm)-**5c**, which were prepared from **1c** having an additional methyl group next to the trimethylsilyl ethyl substituent (Fig. 6a).

The result of the first photocyclization step of **1c** contrasted with that of **1b**, affording a diastereomer mixture of *trans*-(\pm)-**5c** and *cis*-(\pm)-**5c** (84%, 37:63). While there are four stereoisomers possibly generated from the biradical intermediate (Fig. 6b), those having an inward-oriented hydroxy group immediately revert to the starting **1c**, as with the case of **1b**. Unlike with **1b**, however, the stereoisomer (*E,Z*)-**Bc** is not favoured any more than (*Z,Z*)-**Bc** due to the steric repulsion arising between the (trimethylsilyl)methyl group and the added methyl group. Accordingly, conrotatory ring closure occurs with both (*E,Z*)-**Bc** and (*Z,Z*)-**Bc** to give a mixture of *trans*-(\pm)-**5c** and *cis*-(\pm)-**5c**, respectively.

Then, the two diastereomers *trans*-(\pm)-**5c** and *cis*-(\pm)-**5c** were separated by chromatography on silica gel, and each isolated diastereomer was subjected to the second ring-opening reaction. The diastereomer *trans*-(\pm)-**5c** with its hydroxy group directing upward (that is, *trans* to the (trimethylsilyl)methyl substituent) selectively furnished the product *anti*-(\pm)-**4c** with the newly formed C–C bond directing upward (that is, *trans* to the (trimethylsilyl)methyl substituent). On the other hand, the other diastereomer *cis*-(\pm)-**5c** with its hydroxy group directing downward (that is, *cis* to the (trimethylsilyl)methyl substituent) selectively furnished the product *syn*-(\pm)-**4c** with the newly formed C–C bond directing downward (that is, *cis* to the (trimethylsilyl)methyl substituent). Thus, a clear stereospecific

relationship was observed with the pair of diastereomers *trans*-(\pm)-**5c** and *cis*-(\pm)-**5c** to establish that β -aryl elimination occurs in a stereospecific fashion.

Various orthocyclophanes **1** were successfully expanded into metacyclophanes (\pm)-**4** via (\pm)-**5** in a stereospecific manner by sequential action of light and rhodium (Table 1). The carbocyclic ketone **1g** was also transformed to (\pm)-**4g** diastereoselectively, although the photocyclization suffered from the formation of the isomeric benzocyclobutenol (\pm)-**6** (entry 5). The ring expansion of 11-membered cyclic ketone **1h** produced (\pm)-**4h**, which also possessed planar chirality stable at room temperature (entry 6).

Discussion

We have described a ring-expanding pathway from orthocyclophanes **1** to their constitutional isomers, metacyclophanes **2** by means of the sequential action of light and rhodium. Formally, the specific non-strained C–H and C–C bonds are cleaved and rearranged to form a product that is energetically uphill. The energy uptake during photocyclization step drives the transformation forward. Furthermore, the present reaction is successfully extended to the synthesis of metacyclophanes possessing planar chirality to demonstrate that stereospecific chirality transfer takes place during the process of rhodium-catalysed C–C bond cleavage.

Methods

General. All reactions were carried out under an argon atmosphere unless otherwise noted. Photoreactions were carried out using RPR-100 photoreactor (Rayonet). Gel permeation chromatography (GPC) was carried out with a Japan Analytical Industry LC-9204. Flash column chromatography was performed with silica gel 60 N (Kanto). Preparative thin-layer chromatography was performed on silica gel plates with PF254 indicator (Merck). Infrared spectra were recorded on a Shimadzu FTIR DR-8000 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury vx400 (^1H at 400 MHz and ^{13}C at 100 MHz) spectrometer using CDCl_3 (^1H , $\delta = 7.26$) and CDCl_3 (^{13}C , $\delta = 77.0$) as an internal standard unless otherwise noted. High-resolution mass spectra were recorded on a ThermoFisher EXACTIVE (APCI). Optical rotation was measured by a JASCO P-1020 polarimeter with a sodium lamp. HPLC analysis was performed by 4.6×250 mm column. For NMR spectra of compounds **1**, **2**, **4**, **5** and HPLC traces of **4a** and **5a**, please see Supplementary Figs 2–60.

Materials. Preparation of orthocyclophanes **1** is described in Supplementary Methods. Anhydrous THF was purchased from Kanto Chemical Co. Anhydrous

Table 1 | Ring Expansion of 1*.

entry	1	5 [†]	4 [†]
1	<p>1d</p>	<p>(±)-5d 85%, dr > 20:1</p>	<p>(±)-4d 62%, dr > 20:1</p>
2	<p>1e</p>	<p>(±)-5e 82%, dr > 20:1</p>	<p>(±)-4e 60%, dr > 20:1</p>
3	<p>1f</p>	<p>(±)-5f 81%, dr > 20:1</p>	<p>(±)-4f 64%, dr > 20:1</p>
4	<p>1g</p>	<p>(±)-5g 25%, dr > 20:1</p>	<p>(±)-4g 82%, dr > 20:1</p>
5	<p>1h</p>	<p>(±)-5h 81%, dr > 20:1</p>	<p>(±)-4h 73%, dr > 20:1</p>
	<p>(±)-6</p>		

*Reaction conditions: See Supplementary Methods for details.

[†]Isolated yields.

MeOH was purchased from Wako Pure Chemical Industries. Toluene was distilled from sodium/benzophenone ketyl. Methyl vinyl ketone was distilled from K_2CO_3 and $CaCl_2$ prior to use.

Photocyclization of orthocyclophane 1a. An anhydrous THF solution (5.0 ml) of **1a** (21.8 mg, 0.10 mmol) in a Pyrex tube was irradiated under UV light (270–350 nm). After 15 h, the mixture was evaporated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane:AcOEt = 5:1) to afford (\pm)-**5a** (20.0 mg, 0.092 mmol, 92%). 1H NMR: δ = 1.12–1.28 (m, 1H), 1.35–1.64 (m, 5H), 1.69–1.80 (m, 1H), 1.83–1.97 (m, 1H), 2.06–2.19 (m, 1H), 2.28 (ddd, J = 14.4, 8.0, 1.6 Hz, 1H), 3.13–3.24 (m, 2H), 3.91 (ddd, J = 10.4, 8.0, 2.0 Hz, 1H), 4.57 (ddd, J = 10.4, 6.4, 2.0 Hz, 1H), 6.71 (dd, J = 8.4, 0.4 Hz, 1H), 6.77 (dd, J = 7.2, 0.8 Hz, 1H), 7.23 (dd, J = 8.0, 7.2 Hz, 1H); ^{13}C NMR: δ = 21.4, 24.6, 27.5, 28.9, 38.3, 48.4, 72.6, 80.4, 115.0, 117.0, 130.9, 137.2, 142.5 and 154.3; IR (neat): 3,385, 2,920, 1,603, 1,456, 1,273, 1,047 and 775 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{14}H_{19}O_2$, 219.1380; found, 219.1376.

Rhodium-catalysed ring opening of (\pm)-5a**.** A mixture containing [Rh(OH)(cod)] $_2$ (1.1 mg, 2.5 μ mol, 2.5 mol %) and tricyclic benzocyclobutenol (\pm)-**5a** (21.4 mg, 0.10 mmol) in MeOH (0.50 ml) was stirred at 60 °C for 5 h. The reaction mixture was passed through a pad of florisil and eluted with ethyl acetate and evaporated. The residue was purified by preparative thin-layer chromatography on silica gel (Hexane:AcOEt = 20:1) to afford metacyclophane **2a** (15.7 mg, 0.072 mmol, 72%). 1H NMR: δ = 0.98–1.11 (m, 2H), 1.33–1.47 (m, 2H), 1.61–1.79 (m, 4H), 2.26 (dd, J = 6.0, 6.0 Hz, 2H), 3.67 (s, 2H), 4.25 (dd, J = 4.8, 4.8 Hz, 2H), 6.66 (s, 1H), 6.76 (d, J = 7.2 Hz, 1H), 6.78–6.84 (m, 1H), 7.23 (dd, J = 8.0, 8.0 Hz, 1H); ^{13}C NMR: δ = 22.4, 22.7, 24.4, 31.3, 35.8, 50.9, 63.4, 112.1, 116.3, 121.7, 130.4, 135.9, 159.9 and 209.8; IR (neat): 2,922, 1,697, 1,587, 1,161 and 783 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{14}H_{19}O_2$, 219.1380; found, 219.1377.

Synthesis of metacyclophane (\pm)-4a**.** A mixture containing [Rh(OH)(cod)] $_2$ (1.2 mg, 2.5 μ mol, 2.5 mol %), methyl vinyl ketone **3** (81.6 μ l, 1.0 mmol) and (\pm)-**5a** (21.8 mg, 0.10 mmol) in toluene (0.50 ml) was stirred at room temperature for 10 h. The reaction mixture was passed through a pad of florisil using ethyl acetate as the eluent, and then the filtrate was evaporated. The residue was purified by preparative thin-layer chromatography on silica gel (Hexane:AcOEt = 5:1) to afford (\pm)-**4a** (19.9 mg, 0.069 mmol, 69%). 1H NMR: δ = 0.25–0.45 (m, 1H), 0.51–0.68 (m, 1H), 0.77–0.98 (m, 3H), 1.27–1.61 (m, 3H), 1.93–2.13 (m, 5H), 2.50 (ddd, J = 17.6, 9.2, 6.4 Hz, 1H), 2.61 (ddd, J = 17.6, 9.2, 5.6 Hz, 1H), 2.88 (ddd, J = 13.6, 8.8, 6.4 Hz, 1H), 3.30 (ddd, J = 14.4, 9.6, 5.6 Hz, 1H), 3.44 (d, J = 14.6 Hz, 1H), 3.95 (d, J = 14.6 Hz, 1H), 4.08 (ddd, J = 12.0, 6.4, 2.4 Hz, 1H), 4.21 (ddd, J = 11.2, 8.8, 2.0 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 7.14 (dd, J = 8.0, 7.6 Hz, 1H); ^{13}C NMR: δ = 21.8, 22.0, 22.6, 26.4, 28.6, 29.7, 36.7, 44.6, 50.9, 72.1, 120.3, 125.9, 127.8, 134.2, 134.3, 157.6, 207.6 and 209.3; IR (neat): 2,941, 1,705, 1,454, 1,232, 910, 729 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{18}H_{25}O_3$, 289.1798; found, 289.1792.

Synthesis of (+)-4a**.** The racemic mixture of (\pm)-**5a** was separated by chiral preparative HPLC (Daicel CHIRALPAK OZ-H column, hexane:*i*-PrOH = 90:10). [α] $^{25}_D$ = +74.0 (c = 1.1 $\times 10^{-2}$ M in $CHCl_3$).

A mixture containing [Rh(OH)(cod)] $_2$ (1.7 mg, 3.8 μ mol, 2.5 mol %), methyl vinyl ketone (**3**, 122.4 mmol, 1.5 mmol) and (+)-**5a** (33.7 mg, 0.15 mmol, >99:1 *er*) in toluene (0.90 ml) was stirred at room temperature for 10 h. The reaction mixture was passed through a pad of florisil using ethyl acetate as the eluent, and then the filtrate was evaporated. The residue was purified by preparative thin-layer chromatography on silica gel (Hexane:AcOEt = 5:1) to afford metacyclophane (+)-**4a** (32.0 mg, 0.11 mmol, 72%, >99:1 *er*) (Daicel CHIRALPAK IB column, hexane:*i*-PrOH = 90:10, 0.40 ml min^{-1} , retention times: t_1 = 9.322 min, t_2 = 11.09 min), [α] $^{25}_D$ = +68.4 (c = 2.1 $\times 10^{-2}$ M in $CHCl_3$).

Benzocyclobutenol 5b. 1H NMR: δ = 0.13 (s, 9H), 0.81 (dd, J = 14.4, 11.2 Hz, 1H), 1.03 (dd, J = 14.8, 4.0 Hz, 1H), 1.07–1.22 (m, 1H), 1.35–1.61 (m, 5H), 1.64–1.78 (m, 1H), 1.89–2.04 (m, 2H), 2.17–2.30 (m, 1H), 2.36 (br s, 1H), 3.39 (dd, J = 11.2, 4.0 Hz, 1H), 3.82–3.90 (m, 1H), 4.55 (ddd, J = 10.4, 6.0, 1.6 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 7.22 (dd, J = 8.0, 7.2 Hz, 1H); ^{13}C NMR: δ = -0.8, 16.8, 21.2, 25.4, 27.2, 29.1, 34.1, 55.7, 73.0, 82.7, 114.9, 116.5, 130.9, 136.4, 148.1 and 154.4; IR (neat): 3,331, 2,951, 1,601, 1,464, 1,271, 1,244, 1,005 and 854 cm^{-1} ; HRMS (m/z): [M + Na] $^+$ calcd. for $C_{18}H_{28}O_2SiNa$, 327.1751; found, 327.1743.

Metacyclophane 4b. 1H NMR: δ = -0.03 (s, 9H), 0.67–0.82 (m, 1H), 0.83–1.04 (m, 3H), 1.11 (dd, J = 14.8, 7.2 Hz, 1H), 1.17–1.50 (m, 5H), 1.87 (ddd, J = 12.8, 10.0, 8.0 Hz, 1H), 2.11 (s, 3H), 2.25 (ddd, J = 13.2, 10.0, 3.6 Hz, 1H), 2.46 (ddd, J = 18.0, 10.8, 5.2 Hz, 1H), 2.79 (ddd, J = 17.6, 10.4, 5.6 Hz, 1H), 3.23 (ddd, J = 14.0, 10.4, 5.2 Hz, 1H), 3.41 (ddd, J = 13.6, 10.8, 5.6 Hz, 1H), 4.08 (t, J = 7.2 Hz, 1H), 4.13 (ddd, J = 12.0, 12.0, 2.8 Hz, 1H), 4.31 (ddd, J = 11.6, 3.6, 3.6 Hz, 1H), 6.85–6.92 (m, 2H), 7.12 (dd, J = 8.0, 7.6 Hz, 1H); ^{13}C NMR: δ = -1.0, 15.5, 20.3, 21.7, 23.0,

26.3, 26.4, 29.8, 37.9, 45.0, 51.6, 70.3, 119.1, 121.7, 126.9, 133.5, 138.4, 155.8, 207.8 and 209.9; IR (neat): 2,947, 1,709, 1,454, 1,242, 980 and 831 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{22}H_{35}O_3Si$, 375.2350; found, 375.2340.

Benzocyclobutenol 5c. **5c** was obtained as a diastereomer mixture that was separated by preparative thin-layer chromatography on silica gel (hexane:AcOEt = 10:1). *trans*-**5c**. 1H NMR: δ = 0.12 (s, 9H), 0.98 (dd, J = 15.2, 10.4 Hz, 1H), 1.06 (dd, J = 15.6, 3.6 Hz, 1H), 1.10–1.22 (m, 1H), 1.33–1.60 (m, 5H), 1.62–1.77 (m, 1H), 1.86–2.05 (m, 2H), 2.07–2.40 (m, 5H), 3.41 (dd, J = 10.8, 3.6 Hz, 1H), 3.76–3.87 (m, 1H), 4.52 (ddd, J = 10.8, 6.0, 1.6 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H); ^{13}C NMR: δ = -0.8, 15.8, 16.2, 21.5, 25.6, 27.1, 29.0, 34.3, 54.9, 73.1, 82.2, 114.9, 126.2, 131.6, 135.7, 145.8 and 152.3; IR (neat): 3,423, 2,928, 1,618, 1,493, 1,246, 1,020 and 837 cm^{-1} ; HRMS (m/z): [M + Na] $^+$ calcd. for $C_{19}H_{30}O_2SiNa$, 341.1907; found 341.1899. *cis*-**5c**. 1H NMR: δ = -0.09 (s, 9H), 0.88–1.05 (m, 2H), 1.10–1.29 (m, 1H), 1.33–1.60 (m, 5H), 1.62–1.78 (m, 1H), 1.82–2.02 (m, 2H), 2.09–2.29 (m, 5H), 3.33 (dd, J = 10.0, 4.4 Hz, 1H), 3.84 (ddd, J = 10.4, 8.8, 1.6 Hz, 1H), 4.53 (ddd, J = 10.8, 6.4, 2.0 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H); ^{13}C NMR: δ = -0.8, 16.2, 16.4, 21.8, 25.3, 27.3, 28.9, 38.7, 52.4, 73.0, 81.6, 115.4, 126.0, 131.6, 135.9, 147.5 and 152.9; IR (neat): 3,396, 2,926, 1,491, 1,244 and 835 cm^{-1} ; HRMS (m/z): [M + Na] $^+$ calcd. for $C_{19}H_{30}O_2SiNa$, 341.1907; found, 341.1902.

Metacyclophane anti-4c. The reaction was performed at 60 °C. 1H NMR: δ = -0.02 (s, 9H), 0.741.07 (m, 5H), 1.20–1.45 (m, 4H), 1.77–1.90 (m, 2H), 2.12 (s, 3H), 2.19 (s, 3H), 2.25 (ddd, J = 12.0, 4.0, 4.0 Hz, 1H), 2.44 (ddd, J = 18.0, 11.2, 4.4 Hz, 1H), 2.76 (ddd, J = 18.0, 11.2, 5.2 Hz, 1H), 3.23 (ddd, J = 14.4, 11.2, 4.4 Hz, 1H), 3.60 (ddd, J = 14.0, 11.6, 5.6 Hz, 1H), 4.10–4.27 (m, 3H), 6.83 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H); ^{13}C NMR: δ = -1.3, 15.7, 20.6, 20.7, 22.5, 26.4, 26.6, 29.7, 29.8, 41.1, 45.3, 50.7, 71.0, 119.4, 130.5, 132.9, 134.1, 136.9, 153.6, 207.8 and 209.0; IR (neat): 2,930, 1,697, 1,450, 1,248 and 837 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{23}H_{37}O_3Si$, 389.2506; found, 389.2498.

Metacyclophane syn-4c. The reaction was performed at 60 °C in MeOH instead of toluene. 1H NMR: δ = 0.02 (s, 9H), 0.71–0.86 (m, 2H), 0.90–1.16 (m, 2H), 1.16–1.32 (m, 2H), 1.48–1.85 (m, 5H), 2.01–2.14 (m, 4H), 2.34 (ddd, J = 16.4, 11.6, 4.8 Hz, 1H), 2.41 (s, 3H), 2.55 (ddd, J = 16.0, 11.2, 8.4 Hz, 1H), 2.67 (ddd, J = 13.2, 11.6, 4.8 Hz, 1H), 3.16 (ddd, J = 12.8, 10.8, 4.4 Hz, 1H), 3.81 (dd, J = 8.8, 4.4 Hz, 1H), 3.91 (ddd, J = 12.0, 10.0, 1.2 Hz, 1H), 4.31 (ddd, J = 12.4, 5.6, 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H); ^{13}C NMR: δ = -1.0, 16.7, 21.3, 22.0, 22.78, 22.83, 26.6, 29.7, 31.0, 35.8, 45.8, 51.8, 73.9, 119.9, 130.4, 131.3, 135.3, 139.3, 158.5, 207.7 and 209.6; IR (neat): 2,949, 1,711, 1,454, 1,246, 980 and 833 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{23}H_{37}O_3Si$, 389.2506; found, 389.2499.

Benzocyclobutenol 5d. 1H NMR: δ = 1.12–1.30 (m, 1H), 1.38–1.64 (m, 5H), 1.68–1.80 (m, 1H), 1.87–2.03 (m, 1H), 2.05–2.15 (m, 1H), 2.18–2.32 (m, 1H), 2.84 (dd, J = 14.0, 10.0 Hz, 1H), 3.13 (dd, J = 14.0, 6.0 Hz, 1H), 3.70 (dd, J = 10.4, 6.4 Hz, 1H), 3.87 (ddd, J = 10.8, 9.6, 1.6 Hz, 1H), 4.57 (ddd, J = 10.4, 5.6, 1.6 Hz, 1H), 6.48 (d, J = 7.2 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.4, 7.2 Hz, 1H), 7.21–7.27 (m, 1H), 7.28–7.38 (m, 4H); ^{13}C NMR: δ = 21.3, 25.3, 27.3, 29.2, 34.0, 35.7, 60.0, 73.1, 82.5, 115.4, 116.8, 126.0, 128.4, 128.8, 130.9, 136.4, 140.3, 146.4 and 154.4; IR (neat): 3,331, 2,918, 1,601, 1,454, 1,273, 1,009 and 702 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{21}H_{25}O_2$, 309.18549; found, 309.1840.

Metacyclophane 4d. MeOH was employed as a solvent instead of toluene. 1H NMR: δ = -0.32–0.15 (m, 1H), 0.67–0.80 (m, 1H), 0.84–1.11 (m, 3H), 1.13–1.43 (m, 3H), 1.50 (ddd, J = 18.0, 10.8, 4.4 Hz, 1H), 1.81–1.95 (m, 4H), 2.18–2.38 (m, 2H), 3.02 (ddd, J = 13.6, 10.8, 4.8 Hz, 1H), 3.21 (dd, J = 14.0, 10.0 Hz, 1H), 3.29–3.44 (m, 2H), 4.09 (ddd, J = 12.0, 12.0, 2.8 Hz, 1H), 4.20 (dd, J = 9.6, 4.8 Hz, 1H), 4.33 (ddd, J = 11.6, 3.2, 3.2 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 7.10–7.24 (m, 6H); ^{13}C NMR: δ = 20.1, 20.9, 23.0, 25.7, 26.5, 29.7, 34.3, 39.8, 44.6, 58.5, 70.2, 119.5, 121.9, 126.1, 126.8, 128.3, 129.2, 134.6, 135.6, 140.4, 155.2, 207.9 and 209.1; IR (neat): 2,855, 1,715, 1,699, 1,456, 1,038, 978 and 700 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{25}H_{31}O_3$, 379.2268; found, 379.2256.

Benzocyclobutenol 5e. 1H NMR: δ = 1.04–1.22 (m, 1H), 1.33–1.77 (m, 6H), 1.80–2.14 (m, 3H), 2.16–2.30 (m, 1H), 3.43 (dd, J = 9.2, 5.6 Hz, 1H), 3.68 (t, J = 6.8 Hz, 2H), 3.86 (ddd, J = 10.8, 1.6, 1.6 Hz, 1H), 4.51–4.62 (m, 3H), 6.71 (d, J = 6.4 Hz, 1H), 6.72 (d, J = 5.2 Hz, 1H), 7.20 (dd, J = 8.0, 7.2 Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR: δ = 29.3, 25.3, 27.2, 29.1, 29.9, 34.1, 56.5, 69.2, 73.0, 73.1, 82.1, 115.2, 116.6, 127.6, 127.7, 128.4, 131.0, 136.4, 138.4, 146.6 and 154.4; IR (neat): 3,393, 2,928, 1,603, 1,454, 1,271, 1,080, 1,026, 743 and 696 cm^{-1} ; HRMS (m/z): [M + H] $^+$ calcd. for $C_{23}H_{29}O_3$, 353.2111; found, 353.2100.

Metacyclophane 4e. MeOH was employed as a solvent instead of toluene. 1H NMR: δ = -0.29–0.13 (m, 1H), 0.69–0.82 (m, 1H), 0.91–1.10 (m, 3H), 1.15–1.45 (m, 3H), 1.80–1.92 (m, 4H), 2.13–2.24 (m, 1H), 2.30–2.40 (m, 1H), 2.42–2.67 (m, 3H), 3.21 (ddd, J = 13.6, 10.0, 5.6 Hz, 1H), 3.49 (ddd, J = 13.6, 10.4, 5.2 Hz, 1H),

3.57 (*t*, *J* = 5.6 Hz, 2H), 4.12 (*ddd*, *J* = 11.6, 2.4, 2.4 Hz, 1H), 4.27 (*t*, *J* = 7.6 Hz, 1H), 4.35 (*ddd*, *J* = 11.6, 3.2, 3.2 Hz, 1H), 4.44 (*d*, *J* = 11.6 Hz, 1H), 4.48 (*d*, *J* = 12.0 Hz, 1H), 6.81 (*d*, *J* = 8.0 Hz, 1H), 6.91 (*d*, *J* = 8.0 Hz, 1H), 7.14 (*dd*, *J* = 8.0, 8.0 Hz, 1H), 7.22–7.28 (*m*, 3H), 7.29–7.35 (*m*, 2H); ¹³C NMR: δ = 20.1, 21.6, 23.1, 25.9, 26.4, 27.9, 29.5, 39.2, 45.0, 52.1, 67.9, 70.2, 72.7, 119.4, 121.4, 126.9, 127.3, 127.5, 128.4, 134.5, 136.1, 138.4, 155.5, 208.0 and 209.5; IR (neat): 2,943, 1,705, 1,454, 1,240, 1,099 and 733 cm⁻¹; HRMS (*m/z*): [M + H]⁺ calcd. for C₂₇H₃₅O₄, 423.2530; found, 423.2519.

Benzocyclobutenol 5f. ¹H NMR: δ = 0.02 (*s*, 9H), 0.65 (*ddd*, *J* = 14.4, 12.4, 4.4 Hz, 1H), 0.77 (*ddd*, *J* = 14.4, 12.8, 4.8 Hz, 1H), 1.07–1.23 (*m*, 1H), 1.35–1.60 (*m*, 6H), 1.64–1.78 (*m*, 2H), 1.86–2.01 (*m*, 1H), 2.03–2.12 (*m*, 1H), 2.15–2.31 (*m*, 1H), 2.48 (*br s*, 1H), 3.28 (*dd*, *J* = 8.8, 6.0 Hz, 1H), 3.86 (*ddd*, *J* = 10.8, 9.6, 1.6 Hz, 1H), 4.55 (*ddd*, *J* = 10.4, 5.6, 1.6 Hz, 1H), 6.71 (*d*, *J* = 8.4 Hz, 1H), 6.84 (*d*, *J* = 7.2 Hz, 1H), 7.22 (*dd*, *J* = 8.4, 7.2 Hz, 1H); ¹³C NMR: δ = -1.7, 15.6, 21.4, 23.8, 25.3, 27.2, 29.1, 33.7, 62.8, 73.0, 82.3, 115.2, 116.3, 130.8, 136.4, 147.5 and 154.4; IR (neat): 3,385, 2,926, 1,603, 1,456, 1,244 and 833 cm⁻¹; HRMS (*m/z*): [M + Na]⁺ calcd. for C₁₉H₃₀O₂SiNa, 341.1907; found, 341.1899.

Metacyclophane 4f. ¹H NMR: δ = 0.02 (*s*, 9H), 0.42 (*ddd*, *J* = 14.0, 13.2, 4.8 Hz, 1H), 0.53 (*ddd*, *J* = 14.0, 12.8, 4.4 Hz, 1H), 0.69–1.04 (*m*, 4H), 1.18–1.52 (*m*, 4H), 1.82–1.96 (*m*, 2H), 1.97–2.09 (*m*, 1H), 2.11 (*s*, 3H), 2.20 (*ddd*, *J* = 13.6, 10.0, 4.0 Hz, 1H), 2.47 (*ddd*, *J* = 17.2, 10.0, 5.2 Hz, 1H), 2.71 (*ddd*, *J* = 17.6, 10.0, 5.2 Hz, 1H), 3.18 (*ddd*, *J* = 13.6, 10.0, 5.2 Hz, 1H), 3.43 (*ddd*, *J* = 13.6, 10.4, 5.2 Hz, 1H), 3.90 (*dd*, *J* = 8.0, 6.4 Hz, 1H), 4.15 (*ddd*, *J* = 11.6, 11.6, 2.4 Hz, 1H), 4.30 (*ddd*, *J* = 12.0, 3.6, 3.6 Hz, 1H), 6.83 (*d*, *J* = 6.8 Hz, 1H), 6.92 (*d*, *J* = 7.2 Hz, 1H), 7.16 (*dd*, *J* = 8.0, 8.0 Hz, 1H); ¹³C NMR: δ = -1.8, 14.4, 20.6, 21.5, 22.1, 23.0, 26.4, 26.6, 29.9, 38.2, 45.2, 59.5, 70.6, 119.4, 121.2, 127.2, 134.7, 136.7, 156.0, 207.9 and 210.3; IR (neat): 2,939, 1,713, 1,692, 1,452, 1,248 and 837 cm⁻¹; HRMS (*m/z*): [M + H]⁺ calcd. for C₂₃H₃₇O₃Si, 389.2506; found, 389.2495.

Benzocyclobutenol 5g. ¹H NMR: δ = 0.13 (*s*, 9H), 0.75–1.02 (*m*, 3H), 1.07–1.46 (*m*, 6H), 1.48–1.79 (*m*, 4H), 1.94 (*ddd*, *J* = 14.8, 6.0, 2.8 Hz, 1H), 2.08 (*ddd*, *J* = 15.2, 10.8, 5.6 Hz, 1H), 2.65 (*ddd*, *J* = 14.0, 4.0, 4.0 Hz, 1H), 2.79 (*ddd*, *J* = 13.2, 13.2, 4.0 Hz, 1H), 3.29 (*dd*, *J* = 12.0, 3.2 Hz, 1H), 6.96 (*d*, *J* = 7.2 Hz, 1H), 7.05 (*d*, *J* = 8.0 Hz, 1H), 7.23 (*dd*, *J* = 7.6, 7.6 Hz, 1H); ¹³C NMR: δ = -0.8, 16.9, 20.2, 20.5, 20.9, 27.2, 27.5, 28.5, 31.5, 55.1, 85.9, 119.9, 127.3, 129.6, 137.3 and 146.8, 147.1; IR (neat): 3,319, 2,926, 1,246 and 849 cm⁻¹; HRMS (*m/z*): [M + H]⁺ calcd. for C₁₉H₃₁O₂Si, 303.2139; found, 303.2130.

Metacyclophane 4g. The reaction was performed at 60 °C. ¹H NMR: δ = -0.48–0.36 (*m*, 1H), 0.052 (*s*, 9H), 0.46–0.57 (*m*, 1H), 0.69–0.84 (*m*, 3H), 1.13–1.30 (*m*, 4H), 1.48–1.56 (*m*, 1H), 1.67–1.85 (*m*, 3H), 2.09 (*s*, 3H), 2.21 (*ddd*, *J* = 10.0, 7.6, 2.8 Hz, 1H), 2.38–2.57 (*m*, 3H), 3.04 (*ddd*, *J* = 9.2, 3.6, 3.6 Hz, 1H), 3.10–3.16 (*m*, 2H), 3.99 (*t*, *J* = 5.2 Hz, 1H), 7.06 (*dd*, *J* = 5.2, 0.8 Hz, 1H), 7.18 (*dd*, *J* = 5.2, 4.8 Hz, 1H), 7.25 (*d*, *J* = 5.6 Hz, 1H); ¹³C NMR: δ = -0.8, 16.6, 22.9, 23.4, 24.7, 25.06, 25.12, 26.5, 29.8, 32.8, 34.0, 45.4, 53.4, 125.4, 127.0, 130.1, 136.8, 139.8, 141.4, 207.5 and 211.5; IR (neat): 2,945, 1,715, 1,697, 1,248 and 837 cm⁻¹; HRMS (*m/z*): [M + H]⁺ calcd. for C₂₃H₃₇O₂Si, 373.2557; found, 373.2548.

Benzocyclobutenol 5h. ¹H NMR: δ = 0.13 (*s*, 9H), 0.80 (*dd*, *J* = 14.4, 11.2 Hz, 1H), 1.05 (*dd*, *J* = 14.4, 4.0 Hz, 1H), 1.18–1.33 (*m*, 1H), 1.39–2.02 (*m*, 11H), 2.33 (*br s*, 1H), 3.35 (*dd*, *J* = 11.2, 4.0 Hz, 1H), 3.89–4.02 (*m*, 1H), 4.27–4.38 (*m*, 1H), 6.73 (*d*, *J* = 8.4 Hz, 1H), 6.77 (*d*, *J* = 7.2 Hz, 1H), 7.23 (*dd*, *J* = 8.4, 7.2 Hz, 1H); ¹³C NMR: δ = -0.7, 16.7, 23.4, 23.6, 26.8, 27.2, 28.0, 33.8, 55.7, 69.1, 82.7, 112.1, 115.9, 130.6, 135.5, 148.7 and 153.0; IR (neat): 3,385, 2,868, 1,593, 1,474, 1,244, 1,038 and 833 cm⁻¹; HRMS (*m/z*): [M + Na]⁺ calcd. for C₁₉H₃₀O₂SiNa, 341.1907; found, 341.1899.

Metacyclophane 4h. ¹H NMR: δ = 0.06 (*s*, 9H), 0.49–0.62 (*m*, 1H), 0.69–1.05 (*m*, 7H), 1.21–1.38 (*m*, 1H), 1.41–1.56 (*m*, 2H), 1.58–1.72 (*m*, 1H), 1.92 (*ddd*, *J* = 13.2, 8.8, 6.4 Hz, 1H), 2.12 (*s*, 3H), 2.34 (*ddd*, *J* = 13.2, 9.2, 6.0 Hz, 1H), 2.45 (*ddd*, *J* = 17.6, 10.8, 5.2 Hz, 1H), 2.79 (*ddd*, *J* = 17.6, 10.8, 5.6 Hz, 1H), 3.14 (*ddd*, *J* = 13.6, 10.4, 5.2 Hz, 1H), 3.35 (*ddd*, *J* = 13.6, 10.8, 5.2 Hz, 1H), 4.04 (*dd*, *J* = 8.0, 6.4 Hz, 1H), 4.23 (*ddd*, *J* = 12.4, 7.2, 2.8 Hz, 1H), 4.29 (*ddd*, *J* = 12.0, 7.2, 2.4 Hz, 1H), 6.88 (*d*, *J* = 7.6 Hz, 1H), 6.92 (*d*, *J* = 8.4 Hz, 1H), 7.13 (*dd*, *J* = 8.0, 8.0 Hz, 1H); ¹³C NMR: δ = -1.1, 17.6, 20.9, 23.7, 23.8, 26.4, 26.8, 29.5, 29.8, 38.2, 44.3, 51.0, 71.6, 117.1, 121.9, 127.1, 132.1, 139.0, 157.5, 207.9 and 210.8; IR (neat): 2,932, 1,711, 1,246 and 835 cm⁻¹; HRMS (*m/z*): [M + H]⁺ calcd. for C₂₃H₃₇O₃Si, 389.2506; found, 389.2494.

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Author contributions

N.I. and M.M. conceived the concept and prepared the manuscript. S.S. conducted the experiments. DFT calculation was performed by N.I.

Additional information

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