

Transformation of Organic Molecules
Based on Ring Opening of Four-Membered Carbon Skeletons

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Masahiro Murakami at Kyoto University from April 2009 to July 2015. The studies are concerned with transformations of organic molecules through the ring opening of four-membered carbon skeletons.

The author would like to express his sincerest gratitude to Supervisor Professor Masahiro Murakami for his continuous guidance, encouragement, and stimulating discussions throughout this study. All the works in this thesis could be achieved with his constant supervisions.

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Contents

General Introduction		1
Chapter 1	Synthesis of 3,3-Disubstituted α -Tetralones by Rhodium-Catalyzed Reaction of 1-(2-Haloaryl)cyclobutanols	11
Chapter 2	Rhodium-Catalyzed Ring Opening of Benzocyclobutenols with Site-Selectivity Complementary to Thermal Ring Opening	31
Chapter 3	Construction of Tetralin Skeletons Based on Rhodium-Catalyzed Site-Selective Ring Opening of Benzocyclobutenols	51
Chapter 4	Stereospecific Construction of Planar Chirality through Carbon–Carbon Bond Cleavage	71
Chapter 5	Ring Opening of Alkoxybenzocyclobutenes with Site-Selective Hydrogenolysis of C(sp ²)–C(sp ³) Bond	107
List of Publications		127

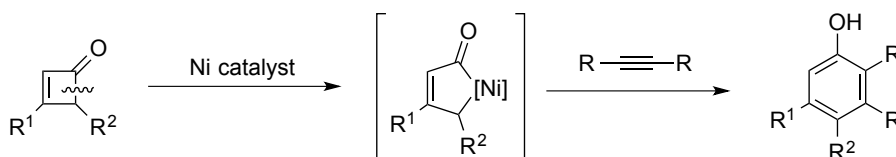
General Introduction

Four-membered ring. Selective cleavage of abundant C–C bonds have attracted a lot of interest in the field of organometallic chemistry, which could provide organic molecules in an atom-economical manner.¹ Although the cleavage of a C–C bond is a challenging subject owing to their thermodynamic stability as well as their kinetic inertness, four-membered ring skeletons are well utilized to access to diverse carbon frameworks via C–C bond cleavage.² This is because the release of strain energy is available to progress an elementary step of the C–C bond cleavage forward thermodynamically.³ In addition, HOMO and LUMO of C–C σ -orbital in four-membered ring are similar to those of C=C π -orbital due to structural distortion. These distinct orbitals assist a metal complex to interact with a C–C bond to reduce the kinetic barrier. There have been a number of publications about C–C bond cleavage of four-membered ring to date,⁴ the author would like to provide a brief introduction about catalytic transformations of cyclobutane derivatives for the background of his thesis.

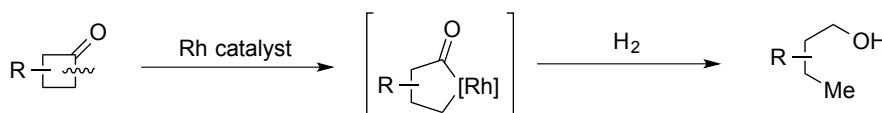
Early works. Catalytic transformations based on the ring opening of a four-membered ring have been developed since around 1990. Liebeskind *et al.* reported a nickel-catalyzed reaction of cyclobutenone derivatives in 1991 (Scheme 1a).⁵ In this case, a nickel complex cleaved a C–C bond of cyclobutenone to afford a substituted phenol through the insertion of alkyne. In 1994, Murakami, Amii, and Ito have found that a rhodium complex also cleaved a C–C bond of cyclobutanone derivatives catalytically (Scheme 1b).⁶ In this report, a rhodium complex was inserted into a C–C bond adjacent to a carbonyl group selectively via oxidative addition. With this result as a trigger, Murakami group has mainly developed the synthetic transformations via the C–C bond cleavage of cyclobutane frameworks with the use of a rhodium catalyst.⁷

Scheme 1. Catalytic transformations via the C–C bond cleavage

(a) Nickel-catalyzed ring opening of cyclobutenone

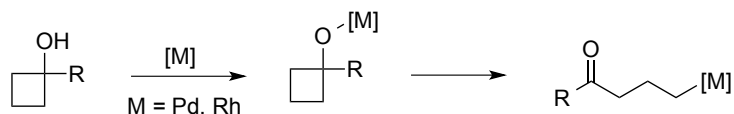


(b) Rhodium-catalyzed ring opening of cyclobutanone

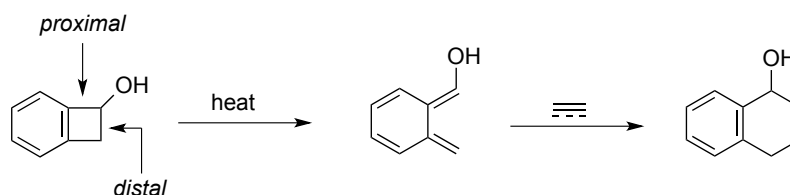


Ring opening of cyclobutanols. Transition metal-catalyzed reactions of cyclobutanols construct a wide variety of carbon skeletons via ring opening of the cyclobutane ring.^{8,9} Mechanistically, these transformations proceed through the formation of a metal cyclobutanolate via ligand exchange, followed by β -carbon elimination in which a carbon atom on γ -position migrates onto metal center with the cleavage of the C–C bond between β - and γ -positions (Scheme 2).¹⁰ Not only the release of the strain but also the generation of the carbonyl group are crucial to proceed this elementary process forward. It may be assumed that an agostic interaction plays an important role for β -carbon elimination although there has been no report about the direct observation of such an interaction.¹¹

In 1999, Uemura *et al.* reported the first example concerned with ring opening of cyclobutanols via β -carbon elimination in the presence of a palladium catalyst.⁸ They also developed the asymmetric synthesis of β -arylated ketone through the enantioselective C–C bond cleavage by a chiral palladium-catalyzed reaction of cyclobutanols with aryl halides.^{8c,d} On the other hand, Murakami group found a rhodium catalyst also induced ring opening of a cyclobutanol.¹² The generating rhodium cyclobutanolate undergoes ring opening through β -carbon elimination to furnish (δ -ketoalkyl)rhodium(I) species. Since this species shows a unique reactivity dependent on the structure of starting materials, there have been developed synthetic transformations based on a rhodium-catalyzed reaction of cyclobutanol derivatives.⁹ The detail will be mentioned in chapter 1.

Scheme 2. Ring opening of cyclobutanols via β -carbon elimination

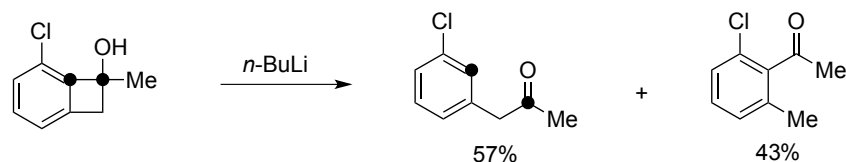
Ring opening of benzocyclobutenols. Unlike cyclobutanols, benzocyclobutenols are known to cleave their C–C bonds in the absence of transition metals. Thermal reaction of benzocyclobutenols induces the distal $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ bond cleavage via 4π electron cyclization reaction (Scheme 3).¹³ Since the generating *o*-quinodimethanes subsequently engage in $[4 + 2]$ cycloaddition with dienophiles,¹⁴ benzocyclobutenol derivatives have been utilized for the synthesis of natural products¹⁵ and functional materials¹⁶.

Scheme 3. Ring opening of benzocyclobutenol under thermal condition

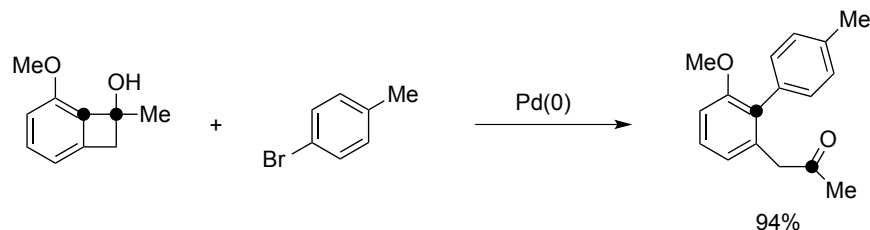
On the other hand, benzocyclobutenols sometimes undergo ring opening with the cleavage of the proximal $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bond in prior to the distal $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ bond.¹⁷ For example, when a chloro-substituted benzocyclobutenol is treated with a base, the proximal $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bond is cleaved (Scheme 4a).^{17b} A palladium catalyst also induces the site-selective ring opening of the proximal $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bond (Scheme 4b).^{17d}

Scheme 4. Ring opening of benzocyclobutenols

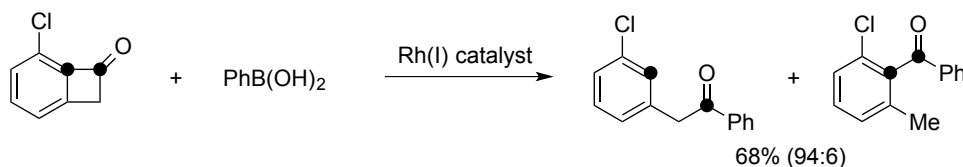
(a) Basic condition



(b) Palladium-catalyzed reaction

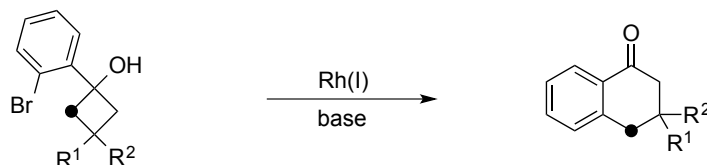


Previously, Murakami group developed a rhodium-catalyzed reaction of 1-chloro-benzocyclobutenone with phenylboronic acid (Scheme 4b).¹⁸ The major ring-opening product is yielded via the cleavage of the proximal C(sp²)-C(sp³) bond. The reaction mechanism is as follows; (1) generation of a phenyl rhodium species by transmetalation, (2) insertion of a carbonyl group into the C(sp²)-Rh bond to furnish a rhodium benzocyclobutanolate, (3) β -carbon elimination to open the cyclobutene ring, and (4) protonation. This result shows that a rhodium benzocyclobutenolate prefers the cleavage of the proximal C(sp²)-C(sp³) bond in prior to the distal C(sp³)-C(sp³) bond. Chapter 2 and after, the author examines a rhodium-catalyzed reaction of benzocyclobutenols, which would generate rhodium benzocyclobutenolates.

Scheme 5. Rhodium-catalyzed reaction of benzocyclobutenones

Overview of this thesis. Herein is disclosed the development of new synthetic transformations based on the ring opening of cyclobutanols and benzocyclobutenols. The outline is shown in the following.

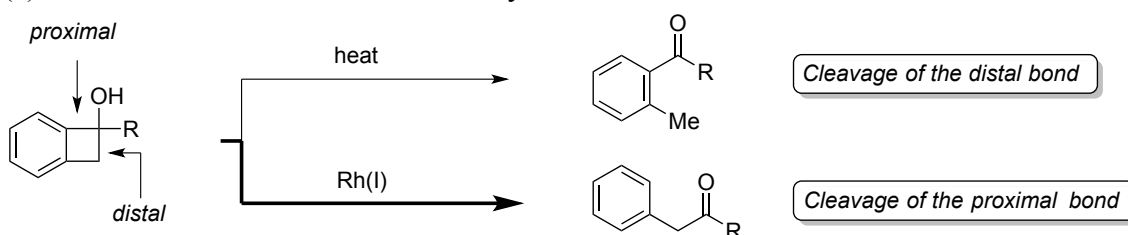
Chapter 1 is shown a rhodium-catalyzed reaction of 1-(2-haloaryl)cyclobutanols to produce 3,3-disubstituted- α -tetralones (Scheme 6). The reaction mechanism is estimated as follows; (1) deprotonation to form a rhodium cyclobutanolate(I), (2) oxidative addition to furnish a five-membered rhodacycle(III), (3) β -carbon elimination to induce ring opening leading to seven-membered rhodacycle(III), and (4) reductive elimination to afford α -tetralone. This reaction can be extended to the asymmetric synthesis of 3,3-disubstituted- α -tetralones through the enantioselective cleavage of the C-C bond in the presence of a chiral rhodium catalyst.

Scheme 6. Rhodium-catalyzed reaction of 1-(2-haloaryl)cyclobutanols

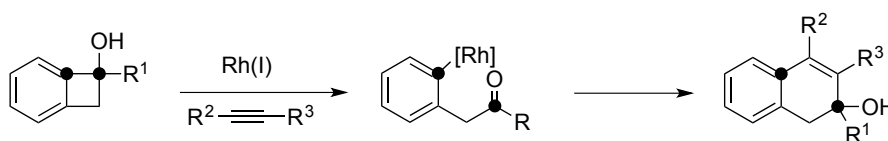
Chapter 2 deals with a rhodium-catalyzed reaction of benzocyclobutenols. In contrast to the thermal reaction, the proximal $C(sp^2)-C(sp^3)$ bond is cleaved selectively in the presence of a rhodium catalyst (Scheme 7a). The reaction mechanism is shown as follows; (1) ligand exchange to furnish a rhodium benzocyclobutenolate, (2) β -carbon elimination to generate arylrhodium species, and (3) protonation to yield the ring-opening product. This site-selective ring opening leads to the development of a new alkyne insertion reaction to form a dihydronaphthalene framework. A triple bond of alkyne is inserted into the proximal $C(sp^2)-C(sp^3)$ bond selectively (Scheme 7b).

Scheme 7. Ring opening of benzocyclobutenols

(a) Thermal reaction vs. Rhodium-catalyzed reaction



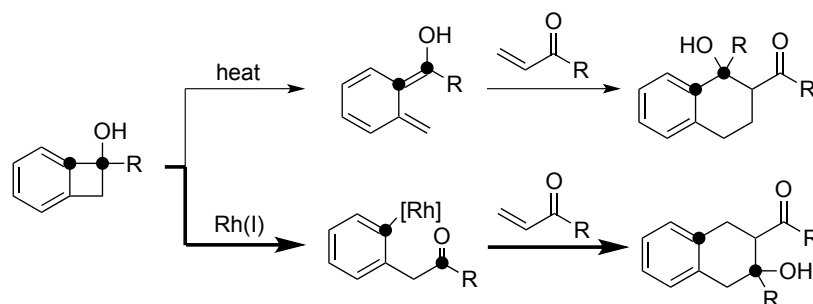
(b) Reaction with alkynes



In chapter 3, the author shows a rhodium-catalyzed reaction of benzocyclobutenols with electron-deficient alkenes to construct tetralin skeletons (Scheme 8). In the same way as a rhodium-catalyzed reaction of benzocyclobutenols with alkynes shown in chapter 2, a double bond of electron-deficient alkene is inserted into the proximal $C(sp^2)-C(sp^3)$ bond with site-selectivity. The produced structures make a remarkable contrast with those available from the identical compounds under thermal reaction

conditions. Mechanistically, the generating arylrhodium species undergoes conjugate addition across an electron-deficient alkene, followed by intramolecular aldol reaction and sequential protonation. The author also demonstrates the synthesis of 2-tetralone skeletons through the rhodium-catalyzed reactions of 1-alkenylbenzocyclobutanols.

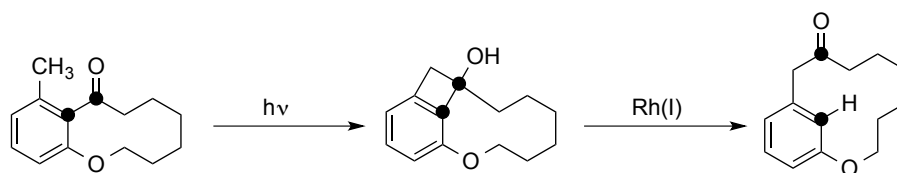
Scheme 8. Thermal ring expansion vs. Rhodium-catalyzed ring expansion



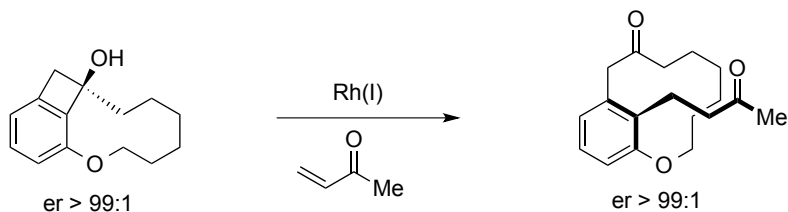
In chapter 4, ring expansion of orthocyclophane to metacyclophane is described (Scheme 9a). This transformation is achieved by sequential action of light and a rhodium catalyst. Non-strained C–H and C–C bonds are cleaved and exchanged in a formal sense without elimination of any leaving groups. Although the product is energetically uphill from the starting material, the endergonic photocyclization step enables to drive the transformation forward. A rhodium-catalyzed reaction of a tricyclic benzocyclobutenol possessing central chirality with methyl vinyl ketone yields a metacyclophane possessing planar chirality (Scheme 9b). This reaction proceeds shown in the following; (1) deprotonation to generate a rhodium benzocyclobutanolate with central chirality, (2) β -carbon elimination to furnish arylrhodium species with planar chirality, and (3) conjugate addition to methyl vinyl ketone to generate oxa(π -allyl)rhodium species, and (4) protonation to yield planar chiral metacyclophane. Central-to-planar chirality transfer occurs during the C–C bond cleavage by β -carbon elimination.

Scheme 9. Synthesis of metacyclophanes

(a) Ring expansion from orthocyclophanes to metacyclophanes



(b) Central-to-planar chirality transfer



In chapter 5, the author examines a palladium-catalyzed hydrogenolysis of alkoxybenzocyclobutenes (Scheme 10). The cyclobutene ring is opened with the cleavage of the proximal C(sp²)–C(sp³) bond selectively although a palladium on carbon catalyst is often utilized to cleave a C(sp³)–C(sp³) bond of small cycloalkane and a C–O bond of benzyl ether.

Scheme 10. Palladium-catalyzed ring opening of alkoxybenzocyclobutenes



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Chapter 1

Synthesis of 3,3-Disubstituted α -Tetralones by Rhodium-Catalyzed Reaction of 1-(2-Haloaryl)cyclobutanols

Abstract

A rhodium-catalyzed reaction of 1-(2-haloaryl)cyclobutanols induced the ring opening of the cyclobutane to form 3,3-disubstituted- α -tetralones. This reaction might proceed through 1) formation of a rhodium(I) cyclobutanolate via ligand exchange, 2) generation of a five-membered rhodacycle(III) via oxidative addition, 3) β -carbon elimination to furnish seven-membered rhodacycle(III), and 4) reductive elimination. Asymmetric synthesis of 3,3-disubstituted- α -tetralone was also achieved in the presence of a chiral rhodium catalyst.

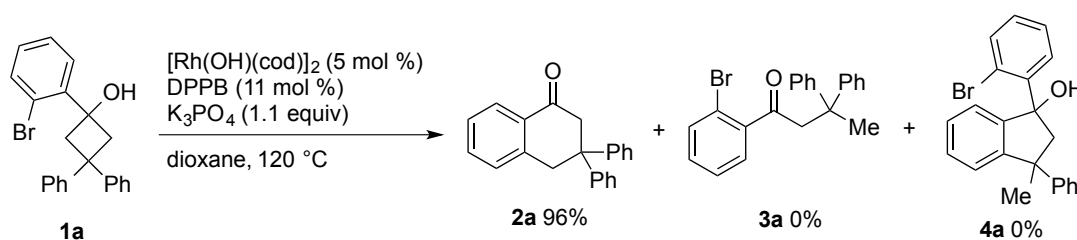
Introduction

Palladium-¹ and rhodium-catalyzed² reactions of cyclobutanols^{3,4} construe a variety of carbon frameworks dependent on the transition metals and the substituents. For example, rhodium cyclobutanolates undergo ring opening by β -carbon elimination to generate (δ -ketoalkyl)rhodium(I) species, with which three pathways are known to proceed. When a 3,3-dialkyl-substituted cyclobutanol is employed as the starting substrate, the resulting alkylrhodium(I) intermediate undergoes a 1,3-rhodium shift to form a rhodium enolate, protonation of which furnishes an acyclic ketone.^{2d} On the other hand, in the case that an aryl group is attached to the 3-position, a 1,4-rhodium shift occurs with the ring-opened (δ -ketoalkyl)rhodium(I) species to furnish an arylrhodium(I) intermediate, which intramolecularly adds to the carbonyl group to afford indanols.^{2b,c} When a cyclobutanol has an alkene or allene substituent at the 1-position, the alkylrhodium(I) intermediate undergoes 1,2-addition across the carbon–carbon double bond, leading to the formation of cyclohexanones or cyclohexenones.^{2e} Herein is disclosed a rhodium-catalyzed reaction of cyclobutanols possessing an *o*-bromoaryl moiety at the 1-position, which furnishes 3,3-disubstituted α -tetralones. Unlike the previous examples, the reaction mechanism involves a rhodium(I)/(III) oxidation/reduction process.

Results and Discussions

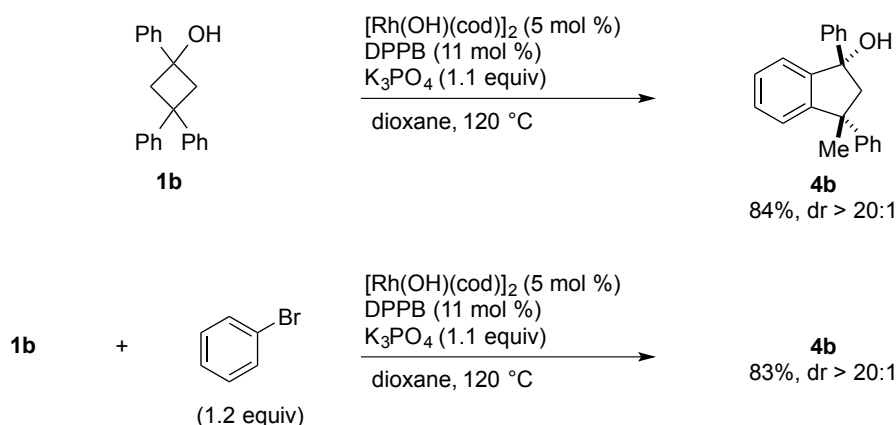
When a dioxane solution of 1-(2-bromophenyl)-3,3-diphenylcyclobutanol (**1a**) was heated at 120 °C in the presence of [Rh(OH)(cod)]₂ (5 mol %), DPPB (11 mol %) and K₃PO₄ (1.1 equiv) for 15 h, α -tetralone **2a** was obtained in 96% isolated yield (Scheme 1).⁵ No formation of acyclic ketone **3a** and indanol **4a** was detected by GC-MS analysis of the reaction mixture. This result suggests that the intermediacy of the ring-opened (δ -ketoalkyl)rhodium species is unlikely.²

Scheme 1. Rhodium-catalyzed reaction of cyclobutanol **1a**

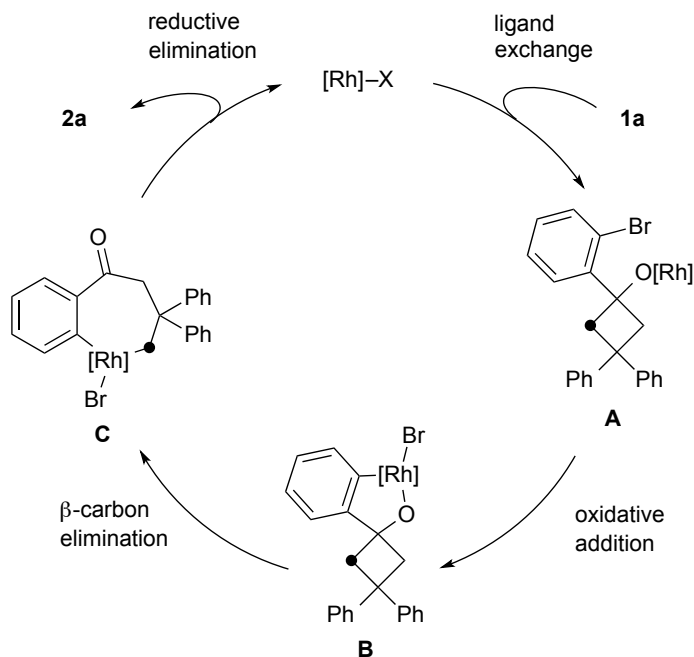


The following experiments were carried out in order to provide information for mechanistic interpretation of the reaction pathway (Scheme 2). When the same reaction conditions were applied to cyclobutanol **1b** without a bromo group on the phenyl ring, indanol **4b** was obtained as a sole product (84% yield).^{2b,c} The reaction of **1b** with bromobenzene also afforded indanol **4b** in 83% yield. Bromobenzene did not react with all rhodium species generated in this catalytic cycle. This result shows in marked contrast to that obtained with a palladium(0) catalyst; bromobenzene participates in the palladium-catalyzed reaction of cyclobutanol **1b** to form a δ -arylated ketone.^{2d} The contrasting results indicate that rhodium(I) is far less reactive towards bromobenzene than palladium(0).⁶ Overall, the presence of the bromo group within the cyclobutanol skeleton dictated the reaction pathway to a new direction, *i.e.*, to the formation of α -tetralones.

Scheme 2. Rhodium-catalyzed reaction of cyclobutenol **1b**

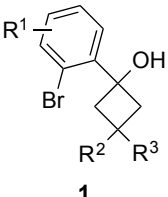
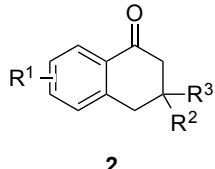
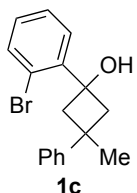
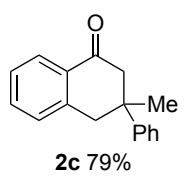
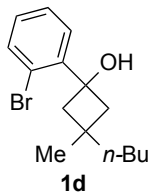
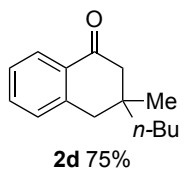
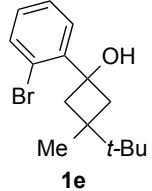
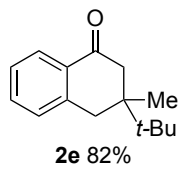
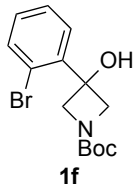
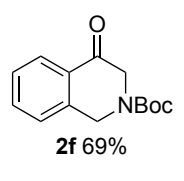
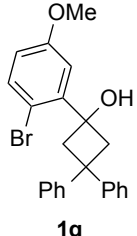
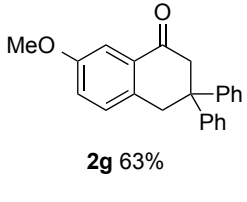


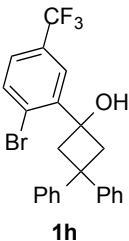
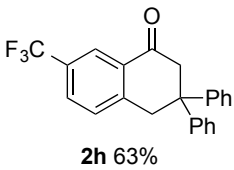
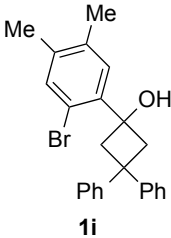
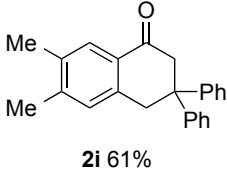
On the basis of these results, the author proposes a possible mechanism for the formation of **2a** from **1a** as depicted in scheme 3. Cyclobutanol **1a** initially reacts with a rhodium(I) complex in the presence of a base to generate rhodium(I) cyclobutanolate **A**. The rhodium(I) center is geometrically constrained in proximity to the bromoaryl group, and thus, an oxidative addition process is facilitated to give five-membered rhodacycle(III) **B**.⁷ Then, the four-membered carbocycle is opened by β -carbon elimination to afford seven-membered rhodacycle(III) **C**.⁸ Finally, reductive elimination provides α -tetralone **2a** with regeneration of the rhodium(I) catalyst.

Scheme 3. A possible mechanism

Other cyclobutanols bearing an *o*-haloaryl group at the 1-position were subjected to the rhodium-catalyzed reaction conditions (Table 1). Cyclobutanols having alkyl and aryl substituents at the 3-position participated in the reaction to give α -tetralones in good yields (entries 1–3). On the other hand, cyclobutanols with the 3-position being unsubstituted provided a complex mixture, probably due to the concurrence of β -hydride elimination with intermediate **C**. The azetidin-3-ol could be employed instead of cyclobutanols to furnish isoquinolinone **2f** in 69% yield (entry 4). Both electron-donating and -withdrawing groups were admitted on the aryl ring (entries 5–7). An iodo counterpart of **1c** underwent the reaction at 100 °C to form **2c** in 72% yield, indicating that aryl iodides were more reactive than aryl bromides. In contrast, the reaction of the chloro analogue of **1a** was much slower. The product **2a** was obtained in 42% yield with the unreacted starting compound remaining even after 48 h. The reaction of the cyclobutanol bearing an *o*-bromobenzyl group gave a complex mixture. These results revealed the importance of the geometrical constraint as well as the reactivity toward oxidative addition of the haloaryl moiety.

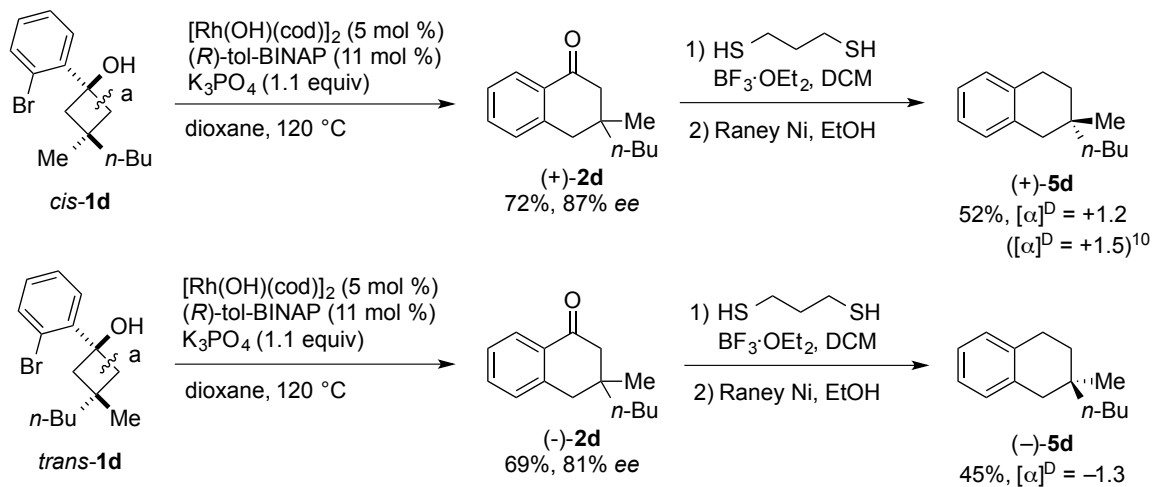
Table 1. Scope of the rhodium-catalyzed reaction of 1-(2-bromoaryl)-cyclobutanols^a

 1 [Rh(OH)(cod)]₂ (5 mol %) DPPB (11 mol %) K₃PO₄ (1.1 equiv) dioxane, 120 °C, 24 h  2		
entry	1	2^b
1 ^{c,d}	 1c	 2c 79%
2 ^c	 1d	 2d 75%
3 ^c	 1e	 2e 82%
4 ^d	 1f	 2f 69%
5 ^e	 1g	 2g 63%

entry	1	2^b
6 ^d	 1h	 2h 63%
7 ^{f,g}	 1i	 2i 61%

^a Reaction conditions: 1.0 equiv cyclobutanol **1**, 5 mol % [Rh(OH)(cod)]₂, 11 mol % DPPB, 1.1 equiv K₃PO₄, dioxane (0.2 M), 120 °C, 24 h unless otherwise noted. ^b Isolated yields. ^c A diastereomer mixture of **1** was used. ^d 11 mol % BINAP was employed instead of DPPB. ^e DMSO was employed instead of dioxane. ^f The reaction was conducted at 0.1 M, 150 °C. ^g Heated for 63 h.

Next was examined the asymmetric synthesis of 3,3-disubstituted- α -tetralones. By screening various chiral ligands, tol-BINAP exhibited a fairly good enantioselectivity (Scheme 4). When *cis*-**1d** was treated with a Rh(I)/(*R*)-tol-BINAP catalyst in dioxane, (+)-**2d** was obtained in 72% yield with 87% *ee*. On the other hand, the other diastereomer *trans*-**1d** afforded the opposite enantiomer (–)-**2d** in 69% yield with 81% *ee*. Both enantiomers were converted to the corresponding tetralins and their absolute configurations were determined by the measurement of optical rotations.⁹ These results suggest that the (*R*)-tol-BINAP ligand favored the cleavage of the bond a located on the right in the drawings of scheme 4, irrespective of the stereochemical arrangement at the 3-position.

Scheme 4. Asymmetric synthesis of 3,3-disubstituted- α -tetralones

Conclusions

The author has developed a rhodium-catalyzed reaction of 3,3-disubstituted 1-(2-haloaryl)cyclobutanols, which provides 3,3-disubstituted α -tetralones with a quaternary carbon center in an enantiomerically enriched form. The author failed to find such chiral α -tetralones by structural search on electronic databases, which was probably owing to the paucity of an appropriate synthetic method. Asymmetric conjugate addition of carbon nucleophiles to α,β -unsaturated carbonyl compounds is an authentic method for introducing a chiral center at the position β to a carbonyl group. However, α -tetralones bearing a chiral quaternary carbon at the 3-position are inaccessible via conjugate addition to dehydrotetralone because 1-naphthol is the more stable tautomer of dehydrotetralone and unreactive as the conjugate acceptor. Therefore, the rhodium-catalyzed reaction shown here would serve as a useful synthetic method for such chiral α -tetralone derivatives.

Experimental section

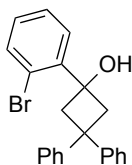
General. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. Infrared spectra were recorded on a Shimadzu FTIR-8400 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury vx400 (^1H at 400 MHz and ^{13}C at 100 MHz) spectrometer using CDCl_3 (^1H , $\delta = 7.26$) 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 and ESI). Optical rotation was measured by a JASCO P-1020 polarimeter with a sodium lamp. HPLC analysis was performed by 4.6 x 250 mm column. Gel permeation chromatography (GPC) was carried out with a Japan Analytical Industry LC-9204. Recycling preparative HPLC was carried out with a Japan Analytical Industry LC-9110 NEXT SERIES. 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).

Materials. 1,4-dioxane was distilled from sodium/benzophenone ketyl. $[\text{Rh}(\text{OH})(\text{cod})]_2$ was prepared according to the literature procedure.¹¹ The cyclobutanones were prepared by [2+2] cycloaddition of the corresponding olefins with dichloroketene and subsequent dechlorination with zinc dust in acetic acid.¹² Cyclobutanol **1b** was prepared according to the literature procedure.^{3d} All other commercially available chemical reagents were used as received without further purification.

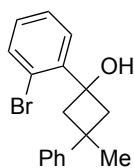
General procedure for the synthesis of 1-(2-haloaryl)cyclobutanols

To a stirred solution of 2-bromoiodobenzene (1.2 equiv) in THF at $-78\text{ }^\circ\text{C}$ was added *i*-PrMgBr in THF (1.2 equiv) slowly. After stirring for 2 h, a solution of cyclobutanone (1.0 equiv) in THF was added dropwise to the reaction mixture at $-78\text{ }^\circ\text{C}$, then warmed to room temperature. After the starting material was consumed, saturated NH_4Cl aq was added. The mixture was extracted with Et_2O , washed with water and brine, dried over Na_2SO_4 , and evaporated. After the purification by flash column chromatography on silica gel or gel permeation chromatography, 1-(2-haloaryl)cyclobutanol was obtained.

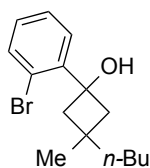
1a:



Purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1), gel permeation chromatography, and recrystallization (DCM and hexane); Yield 32%; IR (neat): 3553, 2986, 762, 710, 696 cm^{-1} ; ^1H NMR: δ = 2.66 (s, 1H), 3.55 (s, 4H), 7.04–7.11 (m, 2H), 7.15–7.25 (m, 6H), 7.31–7.35 (m, 3H), 7.50–7.56 (m, 3H); ^{13}C NMR: δ = 44.3, 48.5, 74.9, 121.7, 125.5, 125.7, 125.9, 126.5, 127.3, 127.6, 128.3, 128.5, 129.1, 134.0, 143.3, 148.9, 149.9; HRMS (APCI): Calcd for $\text{C}_{22}\text{H}_{19}\text{BrOCl}$, $[\text{M}+\text{Cl}]^-$ 413.0302. Found m/z 413.0311.

1c:

Purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) and gel permeation chromatography; Yield 38% (diastereomer mixture); IR (neat): 3422, 2951, 1026, 754, 729, 698 cm^{-1} ; ^1H NMR: δ = 1.31 (s, 3H*), 1.77 (s, 3H), 2.83–2.87 (m, 1H* + 3H), 3.04–3.12 (m, 4H* + 2H), 7.08–7.40 (m, 7H* + 8H), 7.54–7.56 (m, 1H), 7.58–7.61 (m, 1H*), 7.63–7.65 (m, 1H*); ^{13}C NMR: δ = 31.9, 32.2*, 34.8*, 36.4, 47.3, 48.3*, 73.7*, 74.6, 121.5, 122.3*, 124.9, 125.27, 125.30*, 125.4*, 127.3, 127.35*, 127.43, 127.6*, 128.2, 128.3*, 129.0, 129.2*, 133.9, 134.4*, 143.7*, 144.3, 151.1*, 152.0; HRMS (APCI): Calcd for $\text{C}_{17}\text{H}_{17}\text{BrOCl}$, $[\text{M}+\text{Cl}]^-$ 351.0146. Found m/z 351.0155.

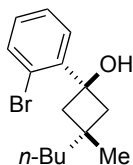
1d:

Purification by flash column chromatography on silica gel (hexane/ethyl acetate = 20/1) and gel permeation chromatography; IR (neat): 3422, 2924, 1003, 754, 727 cm^{-1} ; ^1H NMR: δ = 0.86 (t, J = 6.8 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H*), 0.96 (s, 3H), 1.15–1.38 (m, 9H + 4H*), 1.65–1.69 (m, 2H*), 2.30–2.41 (m, 2H + 2H*), 2.49–2.54 (m, 2H + 2H*), 2.75–2.78 (m, 1H + 1H*), 7.10–7.15 (m, 1H + 1H*), 7.27–7.33 (m, 1H + 1H*), 7.36–7.38 (m, 1H), 7.43–7.45 (m, 1H*), 7.54–7.58 (m, 1H + 1H*); ^{13}C NMR: δ = 14.1, 14.2*, 23.2, 23.3*, 26.4, 26.7, 26.8*, 27.0*, 30.4*, 31.2, 42.4*, 43.4, 46.9, 47.0*, 73.9*,

74.3, 121.8, 122.1*, 127.3*, 127.35, 127.43, 127.5*, 128.89, 128.92*, 134.1, 134.2*, 144.6*, 144.8; HRMS (APCI): Calcd for $C_{15}H_{21}BrOCl$, $[M+Cl]^-$ 331.0459. Found m/z 331.0467.

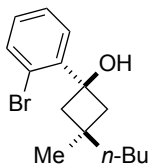
After purification by recycling preparative HPLC, *trans*-**1d** was obtained in 12% yield, and *cis*-**1d** was obtained in 18% yield.

***trans*-1d:**



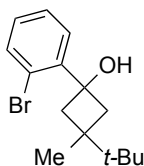
IR (neat): 3422, 2924, 1001, 754, 727 cm^{-1} ; 1H NMR: δ = 0.86 (t, J = 6.8 Hz, 3H), 1.14–1.30 (m, 6H), 1.35 (s, 3H), 2.31–2.35 (m, 2H), 2.49–2.53 (m, 2H), 2.74 (s, 1H), 7.10–7.14 (m, 1H), 7.27–7.32 (m, 1H), 7.36–7.38 (m, 1H), 7.54–7.57 (m, 1H); ^{13}C NMR: δ = 14.1, 23.2, 26.4, 26.7, 31.2, 43.4, 46.9, 74.3, 121.8, 127.36, 127.43, 128.9, 134.1, 144.8; HRMS (APCI): Calcd for $C_{15}H_{21}BrOCl$, $[M+Cl]^-$ 331.0459. Found m/z 331.0464.

***cis*-1d:**



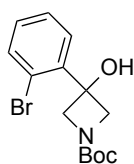
IR (neat): 3422, 2926, 1005, 907, 754, 727 cm^{-1} ; 1H NMR: δ = 0.94 (t, J = 7.2 Hz, 3H), 0.96 (s, 3H), 1.25–1.38 (m, 4H), 1.65–1.69 (m, 2H), 2.37–2.41 (m, 2H), 2.50–2.54 (m, 2H), 2.78 (s, 1H), 7.11–7.15 (m, 1H), 7.28–7.32 (m, 1H), 7.43–7.45 (m, 1H), 7.56–7.58 (m, 1H); ^{13}C NMR: δ = 14.2, 23.3, 26.8, 27.0, 30.4, 42.4, 47.0, 73.9, 122.1, 127.3, 127.5, 128.9, 134.2, 144.6; HRMS (APCI): Calcd for $C_{15}H_{21}BrOCl$, $[M+Cl]^-$ 331.0459. Found m/z 331.0471.

1e:

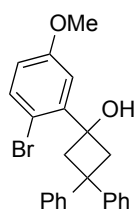


Purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20/1) and gel permeation chromatography; Yield 29% (diastereomer mixture); IR (neat): 3447,

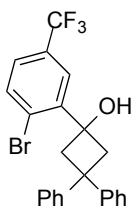
2961, 1159, 1020, 750, 725 cm^{-1} ; ^1H NMR: δ = 0.78 (s, 9H), 0.93 (s, 3H*), 0.94 (s, 9H*), 1.44 (s, 3H), 2.08–2.11 (m, 2H), 2.43–2.46 (m, 2H*), 2.60–2.63 (m, 2H*), 2.75–2.81 (m, 3H + 1H*), 7.09–7.16 (m, 1H + 1H*), 7.27–7.34 (m, 1H + 1H*), 7.37–7.40 (m, 1H), 7.55–7.58 (m, 1H + 1H*), 7.59–7.61 (m, 1H*); ^{13}C NMR: δ = 24.3, 24.4*, 25.0, 25.2*, 28.7*, 33.9, 35.3*, 37.2, 42.1, 42.8*, 71.8*, 73.0, 121.8, 122.6*, 127.2, 127.27*, 127.35, 127.5*, 128.85, 128.95*, 134.2, 134.5*, 144.2, 144.4*; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{21}\text{BrOCl}$, $[\text{M}+\text{Cl}]^-$ 331.0459. Found m/z 331.0466.

1f:

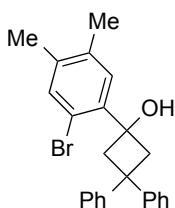
Purified by chromatography on silica gel (hexane/ethyl acetate = 2/1); Yield 66%; IR (neat): 3350, 2976, 1678, 1433, 1111, 748 cm^{-1} ; ^1H NMR: δ = 1.45 (s, 9H), 2.98 (s, 1H), 4.23–4.26 (m, 2H), 4.50–4.53 (m, 2H), 7.19–7.23 (m, 1H), 7.35–7.37 (m, 2H), 7.60–7.62 (m, 1H); ^{13}C NMR: δ = 28.4, 61.5, 73.6, 79.8, 121.9, 127.7, 127.8, 130.1, 134.2, 140.3, 156.3; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{18}\text{BrNO}_3\text{Cl}$, $[\text{M}+\text{Cl}]^-$ 362.0153. Found m/z 362.0163.

1g:

Purified by chromatography on silica gel (hexane/ethyl acetate = 5/1) and gel permeation chromatography; Yield 33%; IR (neat): 3545, 2939, 1464, 1292, 1228, 1026, 745, 694 cm^{-1} ; ^1H NMR: δ = 2.74 (s, 1H), 3.53 (s, 4H), 3.74 (s, 3H), 6.63–6.66 (m, 1H), 6.87–6.88 (m, 1H), 7.05–7.09 (m, 1H), 7.15–7.24 (m, 5H), 7.33 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 8.8 Hz, 1H), 7.49–7.51 (m, 2H); ^{13}C NMR: δ = 44.2, 48.4, 55.5, 74.7, 111.8, 114.0, 114.2, 125.5, 125.7, 125.9, 126.5, 128.3, 128.4, 134.6, 144.3, 148.9, 149.8, 158.8; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{21}\text{BrO}_2\text{Cl}$, $[\text{M}+\text{Cl}]^-$ 443.0408. Found m/z 443.0418.

1h:

Purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) and gel permeation chromatography; Yield 15%; IR (neat): 3566, 3024, 1329, 1167, 1124, 1082, 694 cm^{-1} ; ^1H NMR: δ = 2.67 (br, 1H), 3.58 (s, 4H), 7.07–7.12 (m, 1H), 7.19–7.27 (m, 5H), 7.34–7.39 (m, 3H), 7.52–7.57 (m, 3H), 7.68 (d, J = 8.4 Hz, 1H); ^{13}C NMR = 44.3, 48.2, 74.7, 123.6 (q, J = 270.1 Hz), 124.7 (q, J = 3.7 Hz), 125.68, 125.71, 125.74, 125.8, 126.3, 128.4, 128.5, 129.6 (q, J = 32.9 Hz), 134.6, 144.1, 148.5, 149.2; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{18}\text{BrF}_3\text{OCl}$, $[\text{M}+\text{Cl}]^-$ 481.0176. Found m/z 481.0183.

1i:

Purified by chromatography on silica gel (hexane/ethyl acetate = 5/1) and gel permeation chromatography; Yield 7%; IR (neat): 3566, 2980, 2359, 1447, 1265, 1088, 733, 700 cm^{-1} ; ^1H NMR: δ = 2.19 (s, 3H), 2.21 (s, 3H), 2.63 (br, 1H), 3.56 (s, 4H), 7.07–7.11 (m, 2H), 7.18–7.28 (m, 5H), 7.34–7.39 (m, 3H), 7.54–7.57 (m, 2H); ^{13}C NMR: δ = 18.9, 19.2, 44.3, 48.6, 74.6, 118.0, 125.4, 125.6, 125.9, 126.5, 128.2, 128.4, 128.8, 134.6, 135.6, 137.8, 140.6, 148.9, 150.1; HRMS (APCI): Calcd for $\text{C}_{24}\text{H}_{23}\text{BrOCl}$, $[\text{M}+\text{Cl}]^-$ 441.0615. Found m/z 441.0627.

Rhodium-catalyzed reaction of 1b to form 4b

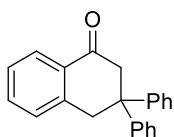
A mixture containing $[\text{Rh}(\text{OH})(\text{cod})]_2$ (2.2 mg, 5.0 μmol , 5.0 mol %), DPPB (4.7 mg, 11 μmol , 11 mol %), K_3PO_4 (23.3 mg, 0.11 mmol), PhBr (18.8 mg, 0.12 mmol), and **1b** (30.0 mg, 0.10 mmol) in 1,4-dioxane (0.50 ml) was stirred at 120 $^\circ\text{C}$ for 24 h. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phase was washed with H_2O and brine, dried over MgSO_4 , and evaporated. The residue was purified by preparative

thin-layer chromatography of silica gel (hexane/ethyl acetate = 10/1) to afford **4b**.

A typical procedure for the rhodium-catalyzed reaction of **1a**

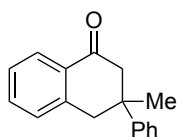
A mixture containing [Rh(OH)(cod)]₂ (2.3 mg, 5.0 μmol, 5.0 mol %), DPPB (4.7 mg, 11 μmol, 11 mol %), K₃PO₄ (23.3 mg, 0.11 mmol), and **1a** (37.9 mg, 0.10 mmol) in 1,4-dioxane (0.50 ml) was stirred at 120 °C for 15 h. After being cooled to room temperature, the reaction mixture was diluted with H₂O and extracted with ethyl acetate (three times). The combined organic phase was washed with H₂O and brine, dried over MgSO₄ and evaporated. The residue was purified by preparative thin-layer chromatography of silica gel (hexane/ethyl acetate = 10/1) to afford **2a** (28.7 mg, 0.096 mmol, 96%)

2a:

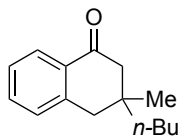


IR (neat): 3024, 1676, 758, 694 cm⁻¹; ¹H NMR: δ = 3.46 (s, 2H), 3.78 (s, 2H), 7.11–7.16 (m, 2H), 7.19–7.33 (m, 10H), 7.45–7.49 (m, 1H), 7.91–7.94 (m, 1H); ¹³C NMR: δ = 42.3, 48.6, 51.0, 126.4, 126.80, 126.83, 126.9, 128.5, 128.9, 132.4, 134.1, 142.1, 145.9, 197.0; HRMS (APCI): Calcd for C₂₂H₁₉O, [M+H]⁺ 299.1430. Found m/z 299.1421.

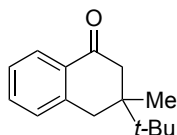
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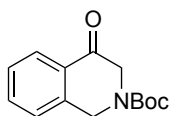
IR (neat): 2920, 1678, 1285, 1028, 768, 698 cm⁻¹; ¹H NMR: δ = 1.42 (s, 3H), 2.87 (d, *J* = 16.4 Hz, 1H), 3.16–3.25 (m, 2H), 3.48 (d, *J* = 16.4 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.26–7.30 (m, 5H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.46–7.50 (m, 1H); ¹³C NMR: δ = 29.5, 40.7, 42.8, 51.3, 125.5, 126.3, 126.7, 126.8, 128.5, 129.1, 131.9, 133.9, 142.3, 146.4, 197.7; HRMS (APCI): Calcd for C₁₇H₁₇O, [M+H]⁺ 237.1274. Found m/z 237.1268.

2d:

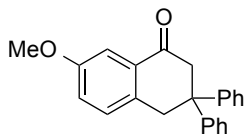
IR (neat): 2928, 1682, 1288, 760 cm^{-1} ; ^1H NMR: δ = 0.86–0.89 (m, 3H), 1.01 (s, 3H), 1.23–1.38 (m, 6H), 2.44–2.49 (m, 1H), 2.52–2.56 (m, 1H), 2.77 (d, J = 16.4 Hz, 1H), 2.91 (d, J = 16.4 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.46–7.50 (m, 1H), 7.99–8.01 (m, 1H); ^{13}C NMR: δ = 14.0, 23.3, 24.9, 25.9, 36.3, 40.9, 41.9, 51.1, 126.5, 126.6, 129.3, 132.0, 133.7, 142.6, 198.7; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{21}\text{O}$, $[\text{M}+\text{H}]^+$ 217.1587. Found m/z 217.1582.

2e:

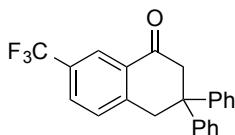
IR (neat): 2964, 1682, 1296, 756 cm^{-1} ; ^1H NMR: δ = 0.92 (s, 3H), 0.99 (s, 9H), 2.51–2.71 (m, 3H), 3.19 (d, J = 16.4 Hz, 1H), 7.22–7.30 (m, 2H), 7.45–7.49 (m, 1H), 7.97–8.00 (m, 1H); ^{13}C NMR: δ = 18.5, 25.2, 35.7, 36.5, 41.0, 46.1, 126.3, 126.4, 129.7, 131.8, 133.6, 143.1, 199.7; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{21}\text{O}$, $[\text{M}+\text{H}]^+$ 217.1587. Found m/z 217.1582.

2f:

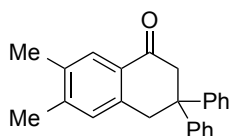
IR (neat): 2980, 1736, 1693, 1418, 1367, 1229, 1159, 1123, 1045, 895, 764, 731 cm^{-1} ; ^1H NMR: δ = 1.47 (s, 9H), 4.33 (s, 2H), 4.76 (s, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H); ^{13}C NMR: δ = 28.3, 44.9, 53.2, 81.0, 126.2, 127.2, 127.6, 127.8, 128.9, 130.4, 134.2, 140.8, 154.2, 192.9; HRMS (ESI): Calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 248.1281. Found m/z 248.1278.

2g:

IR (neat): 2924, 1678, 1495, 1285, 1032, 756, 694 cm^{-1} ; ^1H NMR: δ = 3.44 (s, 2H), 3.72 (s, 2H), 3.78 (s, 3H), 7.04–7.07 (m, 1H), 7.12–7.16 (m, 2H), 7.20–7.25 (m, 9H), 7.407–7.414 (m, 1H); ^{13}C NMR: δ = 41.5, 48.8, 50.8, 55.4, 108.9, 122.3, 126.3, 126.9, 128.5, 130.0, 133.2, 134.6, 146.0, 158.4, 197.0; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{21}\text{O}_2$, $[\text{M}+\text{H}]^+$ 329.1536. Found m/z 329.1528.

2h:

IR (neat): 2924, 1688, 1331, 1256, 1121, 696 cm^{-1} ; ^1H NMR: δ = 3.49 (s, 2H), 3.84 (s, 2H), 7.14–7.27 (m, 10H), 7.46 (d, J = 8.0 Hz, 1H), 7.69–7.72 (m, 1H), 8.20 (s, 1H); ^{13}C NMR: δ = 42.1, 48.5, 50.9, 123.6 (q, J = 270.9 Hz), 124.0 (q, J = 3.7 Hz), 126.6, 126.8, 128.6, 129.7, 130.2 (q, J = 3.7 Hz), 132.7, 145.3, 145.6, 195.7; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{18}\text{F}_3\text{O}$, $[\text{M}+\text{H}]^+$ 367.1304. Found m/z 367.1298.

2i:

IR (neat): 2918, 1670, 700 cm^{-1} ; ^1H NMR: δ = 2.21 (s, 3H), 2.27 (s, 3H), 3.40 (s, 2H), 3.70 (s, 2H), 7.07 (s, 1H), 7.11–7.15 (m, 2H), 7.20–7.24 (m, 8H), 7.68 (s, 1H); ^{13}C NMR: δ = 19.3, 20.2, 41.7, 48.7, 50.9, 126.2, 126.9, 127.5, 128.4, 129.9, 130.3, 135.3, 139.7, 143.9, 146.2, 197.1; HRMS (APCI): Calcd for $\text{C}_{24}\text{H}_{23}\text{O}$, $[\text{M}+\text{H}]^+$ 327.1743. Found m/z 327.1735.

Asymmetric synthesis of (+)-2d

A mixture containing $[\text{Rh}(\text{OH})(\text{cod})]_2$ (2.2 mg, 5.0 μmol , 5.0 mol%), (*R*)-tol-BINAP (7.4 mg, 11 μmol , 11 mol %), K_3PO_4 (23.3 mg, 0.11 mmol), and *cis*-**1d** (29.7 mg, 0.10

mmol) in 1,4-dioxane (0.50 ml) was stirred at 120 °C for 24 h. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate (three times). The combined organic phase was washed with H₂O and brine, dried over MgSO₄, and evaporated. The residue was purified by preparative thin-layer chromatography of silica gel (hexane/ethyl acetate = 10/1) to afford (+)-**2d** (15.7 mg, 0.072 mmol, 72%). The enantiomeric excess was determined to be 87% by chiral HPLC analysis [Daicel CHIRALPAK[®] AS-H column, hexane/*i*-PrOH = 98/2, 0.4 ml/min, retention times: *t*₁ = 6.7 min (major); *t*₂ = 7.0 min (minor)].

Transformation of (+)-**2d** to (+)-**5d**

The CH₂Cl₂ (1.0 ml), propane-1,3-dithiol (40.0 μL, 0.40 mmol), and boron trifluoride diethyl etherate (48.0 μL, 0.38 mmol) were added to the (–)-**2d** (31.5 mg, 0.14 mmol) in the schlenk and the mixture was stirred for 14 h at 23 °C. The reaction mixture was quenched with 2 M aq. NaOH and extracted with Et₂O. The organic layer was washed with water and brine, dried over MgSO₄, and evaporated. The residue was purified by preparative thin-layer chromatography of silica gel (hexane/ethyl acetate = 20/1) to give dithiane. A solution of this dithiane in EtOH (1.0 mL) was added to a suspension of Raney-Ni (1 g) in MeOH (1.00 mL) and stirred for 10 h at room temperature. The mixture was filtered over a celite pad. Hexane was added and the organic layer washed with water and brine, and evaporated. The residue was purified by preparative thin-layer chromatography of silica gel (hexane only) to give (+)-**5d** (14.7 mg, 0.073 mmol, 52 % over 2 steps, [α]^D = +1.2).

Asymmetric synthesis of (–)-**2d**

A mixture containing [Rh(OH)(cod)]₂ (2.2 mg, 5.0 μmol, 5.0 mol%), (*R*)-tol-BINAP (7.4 mg, 11 μmol, 11 mol %), K₃PO₄ (23.3 mg, 0.11 mmol), and *trans*-**1d** (29.7 mg, 0.10 mmol) in 1,4-dioxane (0.50 ml) was stirred at 120 °C for 24 h. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate (three times). The combined organic phase was washed with H₂O and brine, dried over MgSO₄, and evaporated. The residue was purified by preparative thin-layer chromatography of silica gel (hexane/ethyl acetate = 10/1) to afford (–)-**2d** (15.0 mg, 0.069 mmol, 69%). The enantiomeric excess was determined to be 81% by chiral HPLC analysis [Daicel CHIRALPAK[®] AS-H column, hexane/*i*-PrOH = 98/2, 0.4 ml/min, retention times: *t*₁ = 7.4 min (minor); *t*₂ = 7.0 min (major)].

Transformation of (–)-2d to (–)-5d

The CH₂Cl₂ (1.0 ml), propane-1,3-dithiol (40.0 μL, 0.40 mmol), and boron trifluoride diethyl etherate (48.0 μl, 0.38 mmol) were added to the (–)-**2d** (30.0 mg, 0.13 mmol) in the shrenk and the mixture was stirred for 14 h at 23°C. The reaction mixture was quenched with 2 M aq. NaOH and extracted with Et₂O. The organic layer was washed with water and brine, dried over MgSO₄, and evaporated. The residue was purified preparative thin-layer chromatography of silica gel (hexane/ethyl acetate = 20/1) to give dithiane. A solution of this dithiane in EtOH (1.0 mL) was added to a suspension of Raney-Ni (1 g) in EtOH (1.0 mL) and stirred for 10 h at room temperature. The mixture was filtered over a celite pad. Hexane was added and the organic layer washed with water and brine, and evaporated. The residue was purified preparative thin-layer chromatography of silica gel (hexane only) to give (–)-**5d** (11.8 mg, 0.059 mmol, 45 % over 2 steps, $[\alpha]_D^{25} = -1.3$).

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1. (a) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850. (b) Kocovsky, P.; Dunn, V.; Gogoll, A.; Langer, V. *J. Org. Chem.* **1999**, *64*, 101. (c) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (d) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010. (e) Hegedus, L. S.; Ranslow, P. B. *Synthesis* **2000**, 953. (f) Larocsk, R. C.; Reddy, C. K. *Org. Lett.* **2000**, *2*, 3325. (g) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 5089. (h) Trost B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162. (i) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315. (j) Matsuda, T.; Shigeno, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 5219. (k) Schweinitz, A.; Chtchemelinine, A.; Orellana, A. *Org. Lett.* **2011**, *13*, 232.
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5. The results with other ligands at 100 °C for 13 h: PPh₃ (10%), P(*t*-Bu)₃ (10%), IPr (0%), DPPP (23%), BINAP (30%), DPPB (53%).
6. Although the use of palladium complexes was also examined in the reaction of **1a** under various reaction conditions, tetralone **2a** was produced in less than 30% yield together with unidentified byproducts.
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Chapter 2

Rhodium-Catalyzed Ring Opening of Benzocyclobutenols with Site-Selectivity Complementary to Thermal Ring Opening

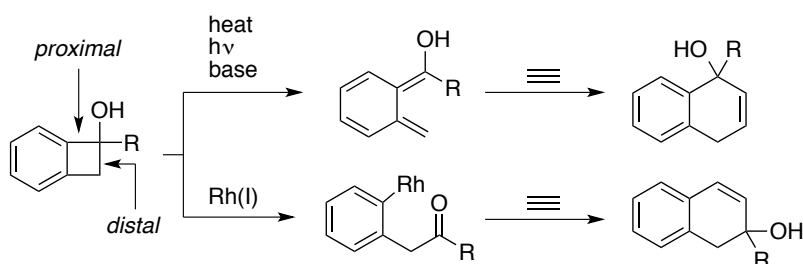
Abstract

Benzocyclobutenols are known to undergo thermal ring-opening reactions with the cleavage of the “distal” carbon–carbon bond to furnish reactive *o*-quinodimethanes. Herein is shown a rhodium-catalyzed ring-opening reaction of benzocyclobutenols, which occurs with the site-selectivity complementary to those of the conventional ring-opening reactions, i.e., with exclusive cleavage of the “proximal” carbon–carbon bond. A new alkyne insertion reaction constructing a dihydronaphthalene framework is developed based on the rhodium-catalyzed proximal carbon–carbon bond cleavage.

Introduction

Cyclobutenes undergo thermal and photochemical ring-opening reactions with cleavage of the $C(sp^3)-C(sp^3)$ bond to form 1,3-dienes.¹ An oxy substituent, in particular an anionic one, accelerates the ring-opening reaction and mediates its own rotational direction (torquoselectivity).² Analogously, benzocyclobutenols undergo ring opening with cleavage of the $C(sp^3)-C(sp^3)$ bond, which the author refers as the “distal” bond (Scheme 1). Heating,³ photo irradiation,⁴ and treatment with a base^{5–7} induce their ring opening to generate reactive *o*-quinodimethanes,⁸ which subsequently react with dienophiles to yield ring expansion products.⁹ This type of [4 + 2] cycloaddition has been utilized for the synthesis of natural products¹⁰ and functional materials.¹¹ On the other hand, Murakami group previously reported a rhodium-catalyzed reaction of phenylboronic acid onto benzocyclobutenone.¹² The resulting rhodium *tert*-benzocyclobutenolate intermediate underwent ring opening with cleavage of the “proximal” bond in prior to the distal bond. This preliminary finding led the author to examine ring opening of benzocyclobutenols under rhodium catalysis in detail. Herein, the author reports a rhodium-catalyzed ring-opening reaction of benzocyclobutenols, which shows a sharp contrast to those of the conventional ring-opening reactions, that is, by exclusive cleavage of the proximal $C(sp^2)-C(sp^3)$ bond.¹³ A new alkyne insertion reaction was also achieved based on this site-selective ring opening (Scheme 1).¹⁴

Scheme 1. Ring opening of Benzocyclobutenols

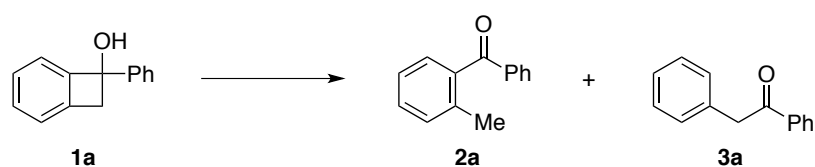


Results and Discussions

Initially, ring opening of **1a** was examined under various reaction conditions (Table 1). Simple heating of **1a** in toluene at 100 °C selectively gave **2a** in 86% yield (entry 1). Addition of a base accelerated the ring-opening reaction to yield only **2a** again (entry 2). Irradiation with UV light (254 nm) also afforded **2a** albeit in 30% yield along with a number of unidentified byproducts (entry 3). On the other hand, when **1a** was heated at

100 °C in toluene in the presence of Rh(acac)(CH₂CH₂)₂ (5 mol %) and P(*t*-Bu)₃ (10 mol %),¹² **2a** and **3a** were obtained as a mixture in 14% and 74% yield respectively. (entry 4). Remarkably, **3a** was obtained as a sole product in 89% yield when [Rh(OH)(cod)]₂ (2.5 mol %) was used in toluene without any additional ligand (entry 5). No 2-methylbenzophenone (**2a**) was detected in the reaction mixture even by GC analysis. The product selectivity was also dependent on a solvent and an additive. The reaction in dioxane under otherwise identical conditions afforded a mixture of **2a** and **3a** with a ratio of 21:79 (entry 6). The addition of 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr) to [Rh(OH)(cod)]₂ yielded **2a** without the formation of **3a** (entry 7).

Table 1. Ring opening of **1a**^a



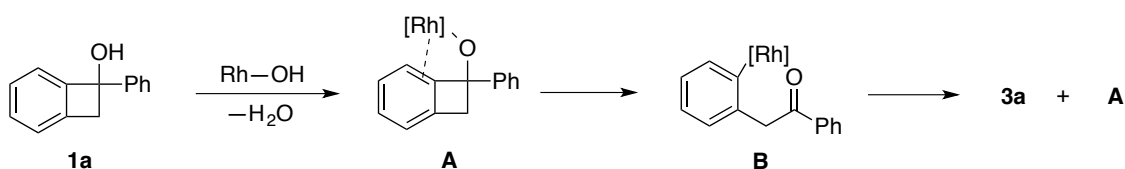
entry	conditions	yields of 2a /% ^b	yields of 3a /% ^b
1	toluene, 100 °C	86	0
2	NaOH aq, dioxane, rt	87	0
3	<i>hν</i> , benzene, rt	30 ^c	0
4	Rh(acac)(CH ₂ CH ₂) ₂ (5 mol %) P(<i>t</i> -Bu) ₃ (10 mol %), toluene, 100 °C	14	74
5	[Rh(OH)(cod)] ₂ (2.5 mol %) toluene, 100 °C	0	89
6	[Rh(OH)(cod)] ₂ (2.5 mol %) dioxane, 100 °C	20	74
7	[Rh(OH)(cod)] ₂ (2.5 mol %) IPr (12 mol %), toluene, 100 °C	80	0

^a Benzocyclobutenol **1a** (0.20 mmol), solvent (1.0 mL). ^b Isolated yields. ^c NMR yield.

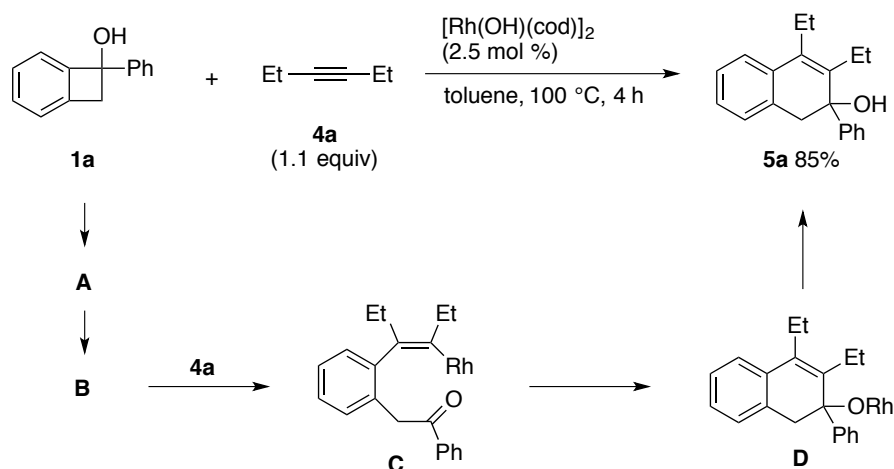
These results demonstrated possibility to switch the ring opening site completely from the distal C(sp³)–C(sp³) bond to the proximal C(sp²)–C(sp³) bond. The author proposes the following mechanistic explanation (Scheme 2). Initially, rhodium hydroxide deprotonates **1a** to form rhodium(I) benzocyclobutenolate **A**. It is assumed that the arene moiety intramolecularly π -coordinates to the rhodium center, as is the case with Rh(PEt₃)₂(OCPh₃).¹⁵ This coordination would assist the migration of the sp²

carbon onto the rhodium in preference to that of the sp^3 carbon, thereby releasing the structural strain and forming a carbonyl group. The superior π -accepting character of the 1,5-cyclooctadiene ligand would facilitate the binding of the arene moiety. The generated arylrhodium species **B** undergoes protonation with **1a** or H_2O to form the benzyl phenyl ketone (**3a**) together with regeneration of the rhodium alkoxide **A**. On the other hand, the ionic character of the rhodium benzocyclobutenolate is augmented in dioxane to partially cause anion-induced thermal ring opening. The strongly binding IPr ligand would occupy the fourth binding site of rhodium of **A** to discourage the π -coordination of the arene, thus suppressing the formation of **3a**.

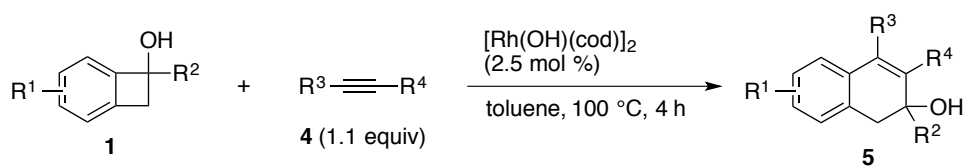
Scheme 2. Plausible mechanism

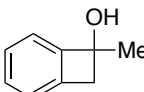
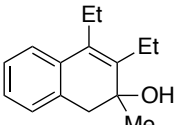
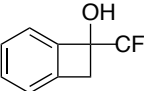
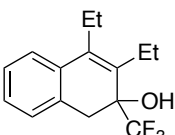
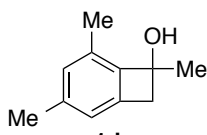
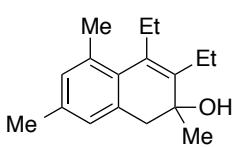
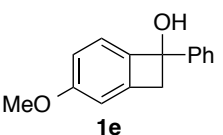
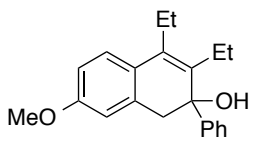
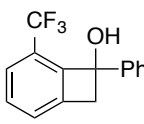
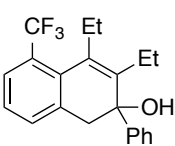
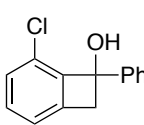
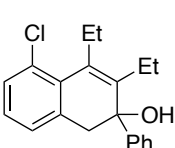
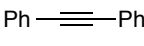
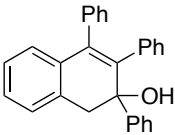


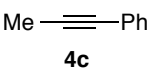
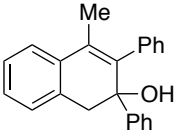
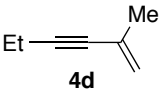
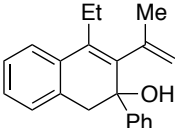
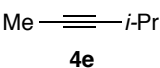
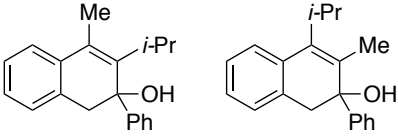
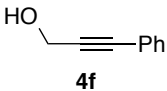
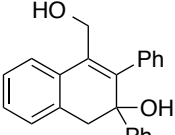
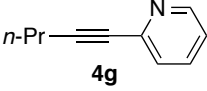
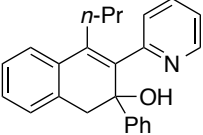
Next, the author examined an alkyne insertion reaction by carrying out the rhodium-catalyzed ring opening of **1a** in the presence of 3-hexyne (Scheme 3). The reaction mixture containing 3-hexyne was heated in toluene at 100 °C for 4 h to furnish dihydronaphthalene **5a** in 85% yield. Mechanistically, the ring-opened arylrhodium(I) intermediate **B** undergoes not protonation but 1,2-addition across the carbon–carbon triple bond. The resulting alkenylrhodium(I) **C** adds back onto the carbonyl group in a 6-exo fashion. Alkoxyrhodium(I) **D** is then protonated to give dihydronaphthalene **5a** with regeneration of rhodium benzocyclobutenolate **A**. Overall, the alkyne **4a** is inserted into the proximal $C(sp^2)-C(sp^3)$ bond of **1a** with site-selectivity to produce a formal [4 + 2] cycloadduct which is contrast markedly with that available through *o*-quinodimethane intermediates.^{8,9}

Scheme 3. Rhodium-catalyzed reaction of **2a** with 3-hexyne (**4a**)

The six-membered ring forming reaction proceeded successfully with various combinations of benzocyclobutenols **1** and alkynes **4** to demonstrate the generality of the unique site-selective insertion (Table 2). Even the *ortho*-substituted derivative **1d** showed the same site-selectivity to give dihydronaphthalene **5d** in 79% yield (entry 3). The presence of electron-donating methoxy and -withdrawing trifluoromethyl groups on the benzene ring scarcely affected the reaction (entries 4 and 5). A chloro group remained intact (entry 6). High regioselectivities were observed with unsymmetrical alkynes bearing one aryl or vinyl substituent (entries 8 and 9), which was located at the β -position (next to the hydroxyl group) of the resulting dihydronaphthalene skeleton. On the other hand, the unsymmetrical dialkyl-substituted alkyne **4e** gave a mixture of regioisomers with the ratio of 75:25 (entry 10). The regioselectivities observed with these unsymmetrical alkynes were similar to previous example in which *o*-carbonyl-substituted arylrhodium species intermolecularly added onto alkynes.¹⁶ An unprotected hydroxyl group and a pyridine moiety were allowed in the alkynes (entries 11 and 12). Insertion of terminal alkynes such as phenylethyne failed due to rapid self-oligomerization.

Table 2. Insertion of alkynes into benzocyclobutenols ^a

entry	1	4	5 ^b
1	 1b	4a	 5b 69%
2	 1c	4a	 5c 80%
3	 1d	4a	 5d 79%
4	 1e	4a	 5e 89%
5	 1f	4a	 5f 78%
6	 1g	4a	 5g 85%
7	1a	 4b	 5h 82%

entry	1	4	5 ^b
8	1a	 4c	 5i 82% (>95:5)
9	1a	 4d	 5j 96% (>95:5)
10	1a	 4e	 5k 5l 85% (75:25)
11	1a	 4f	 5m 91% (>95:5)
12	1a	 4g	 5n 89% (>95:5)

^a Reaction conditions: benzocyclobutenol **1** (0.20 mmol), alkyne **4** (1.1 equiv), [Rh(OH)(cod)]₂ (2.5 mol %), toluene (1.0 mL), 100 °C, 4 h. ^b Isolated yields. Regioisomeric ratios in parentheses.

Conclusions

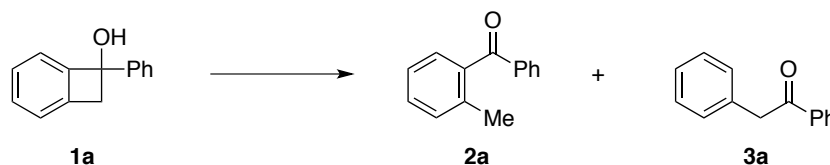
The author has shown that [Rh(OH)(cod)]₂ induces ring opening of benzocyclobutenols with site-selective cleavage of the proximal C(sp²)-C(sp³) bond. This site-selectivity is complementary to that of the conventional ring-opening reactions. A new alkyne insertion reaction constructing a dihydronaphthalene framework was developed based on the unique ring opening.

Experimental section

General. All reactions were carried out under an argon atmosphere in oven-dried glassware with standard Schlenk techniques. Photoreactions were conducted with Rayonet RPR-100. IR measurements were performed on a FTIR SHIMADZU DR-8000. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-vx400 (^1H at 400.44 MHz and ^{13}C at 100.69 MHz) spectrometer. NMR data were obtained in CDCl_3 , acetone- d_6 , C_6D_6 , and CD_3CN . Proton chemical shifts were referenced to the residual proton signal of the solvent at 7.26 ppm (CHCl_3), 2.09 ppm (acetone), 7.15 ppm (benzene), and 1.96 ppm (CH_3CN). Carbon chemical shifts were referenced to the carbon signal of the solvent at 77.0 ppm (CHCl_3), 205.87 ppm (acetone), 128.62 ppm (benzene), and 118.26 ppm (CH_3CN). High-resolution mass spectra were recorded on a Thermo Scientific Exactive (ESI) spectrometer. Flash column chromatography was performed with silica gel 60N (Kanto). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck). Gel permeation chromatography (GPC) was carried out with a Japan Analytical Industry LC-908.

Materials. Toluene and 1,4-dioxane were distilled from sodium/benzophenone ketyl. Anhydrous THF and anhydrous CH_2Cl_2 were purchased from Kanto Chemical Co. Distilled water was purchased from Nacalai Tesque. The following chemicals were synthesized according to the literature procedures; $[\text{Rh}(\text{OH})(\text{cod})]$,^{17a} 1-phenylbenzo cyclobutenol **1a**,^{17b} *o*-trifluoroacetylto luene **A**,^{17c} 1,4,6-trimethyl-benzocyclobutenol **1d**,^{17d} 4-methoxybenzocyclobutenol **B**,^{17e} 6-trifluoromethyl-1-phenylbenzocyclobute none,^{17f} and 6-chlorobenzocyclobutenone^{17g}. All other chemicals were available from commercial sources and were used as received without further purification.

Procedures for the ring-opening reaction of benzocyclobutenol **1a** (Table 1)



Thermal reaction (entry 1)

A solution of benzocyclobutenol **1a** (39.2 mg, 0.20 mmol) in toluene (1 mL) was stirred at 100 °C for 15 h. After the reaction mixture was cooled to room temperature, concentrated under reduced pressure. The residue was purified by preparative thin-layer

chromatography (hexane/ethyl acetate = 10/1) to give 2-methylbenzophenone **2a** (33.7 mg, 0.17 mmol, 86%).

Basic condition (entry 2)

A solution of benzocyclobutenol **1a** (39.2 mg, 0.20 mmol), sodium hydroxide (4.0 mg, 0.10 mmol, 0.50 equiv), and distilled water (10 μ L) in dioxane (1 mL) was stirred at room temperature for 12 h. Then, water was added to the reaction mixture. The resulting aqueous solution was extracted with ethyl acetate (3 x 4 mL). The combined extracts were washed with H₂O and brine and dried over MgSO₄. The solvent removed by reduced pressure and the residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 10/1) to give 2-methylbenzophenone **2a** (34.1 mg, 0.17 mmol, 87%).

Photoreaction (entry 3)

After a solution of benzocyclobutenol **1a** (39.2 mg, 0.20 mmol) in benzene (5 mL) was irradiated for 12 h with UV light (λ = 254 nm), the solvent was removed under reduced pressure to give 2-methylbenzophenone **2a** (30%, NMR yield).

Rhodium-catalyzed reaction (entry 4)

A solution of Rh(acac)(CH₂CH₂)₂ (2.6 mg, 10 μ mol, 5.0 mol %) and P(*t*-Bu)₃ (4.0 mg, 20 μ mol, 10 mol %) in toluene (1 mL) was stirred at 100 °C for 2 h. The reaction mixture was added to benzocyclobutenol **1a** (39.2 mg, 0.20 mmol, 1.0 equiv) and the solution was stirred at 100 °C for 24 h. After cooled to room temperature, the reaction mixture was passed through a pad of Florisil[®] with ethyl acetate as the eluent. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 10/1) to give 2-methylbenzophenone **2a** (5.5 mg, 0.028 mmol, 14%) and benzyl phenyl ketone **3a** (29.0 mg, 0.15 mmol, 74%).

Rhodium-catalyzed reaction (entry 5)

A solution of [Rh(OH)(cod)]₂ (2.3 mg, 5.0 μ mol, 2.5 mol %) and benzocyclobutenol **1a** (39.2 mg, 0.20 mmol, 1.0 equiv) in toluene (1 mL) was stirred at 100 °C for 1 h. After cooled to room temperature, the reaction mixture was passed through a pad of Florisil[®] with ethyl acetate as the eluent. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography

(hexane/ethyl acetate = 10/1) to give benzyl phenyl ketone **3a** (34.9 mg, 0.18 mmol, 89%).

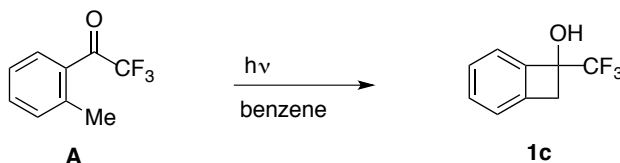
Rhodium-catalyzed reaction (entry 6)

A solution of $[\text{Rh}(\text{OH})(\text{cod})]_2$ (2.2 mg, 5.0 μmol , 2.5 mol %) and benzocyclobutenol **1a** (39.2 mg, 0.20 mmol, 1.0 equiv) in dioxane (1 mL) was stirred at 100 °C for 3 h. After cooled to room temperature, the reaction mixture was passed through a pad of Florisil[®] with ethyl acetate as the eluent. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 20/1) to give 2-methylbenzophenone **2a** (7.9 mg, 0.040 mmol, 20%) and benzyl phenyl ketone **3a** (29.1 mg, 0.15 mmol, 74%).

Rhodium-catalyzed reaction (entry 7)

A solution of $[\text{Rh}(\text{OH})(\text{cod})]_2$ (2.3 mg, 5.0 μmol , 2.5 mol %) and IPr (10.2 mg, 10 mmol, 12 mol %) in toluene (1.0 mL) was stirred at room temperature for 4 h. The reaction mixture was added to benzocyclobutenol **1a** (39.0 mg, 0.20 mmol, 1.0 equiv) in toluene (1 mL) was stirred at 100 °C for 15 h. After cooled to room temperature, the reaction mixture was passed through a pad of Florisil[®] with ethyl acetate as the eluent. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 10/1) to give benzyl phenyl ketone **3a** (31.7 mg, 0.16 mmol, 80%).

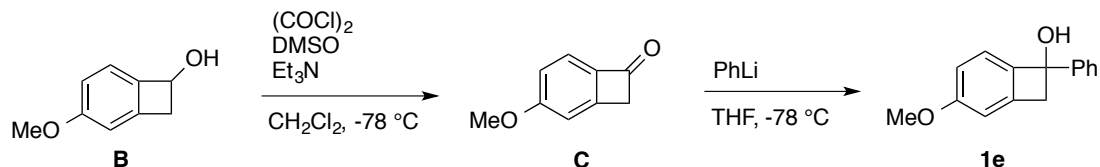
A procedure for the synthesis of **1c**



A solution of *o*-trifluoroacetyltoluene **A** (39 mg, 0.20 mmol) in benzene (1 mL) was irradiated for 6 h with UV light ($\lambda = 300 \text{ nm}$). After complete conversion of **A**, the solvent was removed under reduced pressure to give a quantitative yield of benzocyclobutenol **1c** as colorless oil; IR (ATR): 3349, 1312, 1153, 1016, 756 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6): $\delta = 2.34$ (br s, 1H), 2.76 (dd, $J = 14.4, 0.8 \text{ Hz}$, 1H), 3.39 (d, $J = 14.4 \text{ Hz}$, 1H), 6.75–6.78 (m, 1H), 6.90–7.04 (m, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 42.4, 78.9$ (q, $J = 32.3 \text{ Hz}$), 122.7, 124.2, 126.1 (q, $J = 279.6 \text{ Hz}$), 128.8, 131.7, 142.6,

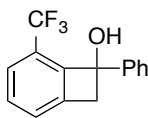
142.8; HRMS (ESI): Calcd for $C_9H_6F_3O$, $[M-H]^-$ 187.0376. Found m/z 187.0371.

A procedure for the synthesis of benzocyclobutenol **1e**

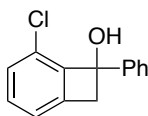


To a solution of oxalyl chloride (1.4 g, 11 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL), dimethyl sulfoxide (1.6 mL, 22 mmol, 2.2 equiv) was added dropwise at $-78\text{ }^\circ\text{C}$. After the reaction mixture was stirred at this temperature for 1 h, a solution of 4-methoxybenzocyclobutenol **B** (1.5 g, 10 mmol) in CH_2Cl_2 (5 mL) was added dropwise. Additional stirring at $-78\text{ }^\circ\text{C}$ for 1 h, Et_3N (3.1 mL, 22 mmol, 2.2 equiv) was added dropwise and the reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 1 h. The resulting mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were washed with H_2O and brine and dried over $MgSO_4$. The solvent removed by reduced pressure and the residue was purified by column chromatography (hexane/ethyl acetate = 10/1) to give **C** (1.3 g, 8.9 mmol, 89%).

To a solution of **C** (740 mg, 5.0 mmol) in THF (10 mL), a solution of PhLi in cyclohexane-diethylether (1.07 M, 5.1 mL, 5.5 mmol) was added dropwise at $-78\text{ }^\circ\text{C}$. After stirred at this temperature for 30 min, the reaction mixture was warmed to room temperature. The resulting mixture was quenched by addition of a saturated NH_4Cl solution and the aqueous solution was extracted with ethyl acetate. The combined extracts were washed with H_2O and brine and dried over Na_2SO_4 . The solvent removed by reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate = 5/1) to give benzocyclobutenol **1e** as colorless oil (740 mg, 3.3 mmol, 66%); IR (ATR): 3396, 2924, 1587, 1475, 1273, 1072, 698 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 2.68 (s, 1H), 3.52 (d, J = 14.0 Hz, 1H), 3.58 (d, J = 14.0 Hz, 1H), 3.82 (s, 3H), 6.81 (s, 1H), 6.85–6.88 (m, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.28–7.30 (m, 1H), 7.32–7.36 (m, 2H), 7.46–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.2, 55.4, 80.5, 109.3, 114.5, 122.9, 125.6, 127.2, 128.1, 140.9, 143.0, 143.8, 161.1; HRMS (ESI): Calcd for $C_{15}H_{14}O_2$, $[M+H]^+$ 227.1067. Found m/z 227.1060.

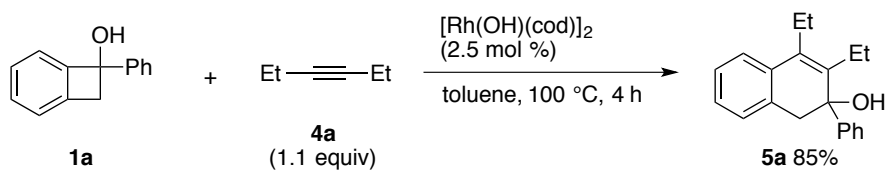
1f:

According to the procedure analogous to that described for **1e**, **1f** (1.2 g, 4.6 mmol, 91%) was prepared from 6-trifluoromethyl-1-phenylbenzocyclobutenone (930 mg, 5.0 mmol). Purified by column chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3420, 3061, 1616, 1448, 1323, 1119, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.95 (s, 1H), 3.56 (d, J = 14.4 Hz, 1H), 3.67 (d, J = 14.0 Hz, 1H), 7.28–7.54 (m, 8H); ^{13}C NMR (100 MHz, acetone- d_6): δ = 51.6, 81.2, 124.0 (q, J = 270.2 Hz), 124.4 (q, J = 34.4 Hz), 124.6 (q, J = 4.4 Hz), 125.2, 127.3, 128.2, 128.4, 130.3, 144.1, 144.7, 148.8; HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{15}\text{F}_3\text{ON}$, $[\text{M}+\text{NH}_4]^+$ 282.1100. Found m/z 282.1093.

1g:

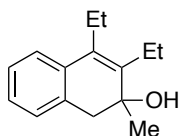
According to the procedure analogous to that described for **1e**, **1g** (970 mg, 4.2 mmol, 83%) was prepared from 6-chloro-1-phenylbenzocyclobutenone (760 mg, 5.0 mmol). Purified by column chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3362, 2928, 1585, 1448, 1134, 758, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.84 (br s, 1H), 3.55 (d, J = 14.0 Hz, 1H), 3.59 (d, J = 14.4 Hz, 1H), 7.14 (dd, J = 7.2, 0.8 Hz, 1H), 7.25–7.40 (m, 5H), 7.50–7.53 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 49.5, 81.4, 122.3, 125.5, 126.8, 127.78, 127.80, 128.4, 131.1, 142.5, 144.2, 145.1; HRMS (ESI): Calcd for $\text{C}_{14}\text{H}_{11}\text{ClONa}$, $[\text{M}+\text{Na}]^+$ 253.0391. Found m/z 253.0387.

Rhodium-catalyzed reaction of **1a** and **4a**

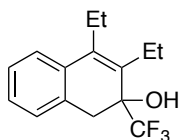


To an oven-dried flask equipped with a stirrer bar was added $[\text{Rh}(\text{OH})(\text{cod})]_2$ (2.3 mg, 5.0 μmol , 2.5 mol %). The flask was capped with a rubber septum, evacuated and

refilled with argon three times. Then, a solution of 1-phenylbenzocyclobutenol **1a** (39 mg, 0.20 mmol, 1.0 equiv) and 3-hexyne (18 mg, 0.22 mmol, 1.1 equiv) in dry toluene (1 mL) was added by syringe. After stirred at 100 °C for 4 h, the reaction mixture was cooled to room temperature. The resulting mixture was passed through a pad of Florisil[®] and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) to give dihydronaphthalene **5a** as colorless oil (47 mg, 0.17 mmol, 84%); IR (ATR): 3460, 2964, 1726, 1447, 1240, 1038, 766, 700 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆): δ = 1.10 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.6 Hz, 3H), 2.21–2.30 (m, 1H), 2.44–2.53 (m, 1H), 2.66–2.81 (m, 2H), 3.11 (d, *J* = 15.2 Hz, 1H), 3.37 (d, *J* = 15.2 Hz, 1H), 4.33 (s, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 7.01–7.05 (m, 1H), 7.13–7.24 (m, 4H), 7.40–7.45 (m, 3H); ¹³C NMR (100 MHz, acetone-d₆): δ = 14.2, 15.0, 21.6, 22.0, 47.3, 76.7, 123.4, 126.4, 126.6, 127.11, 127.14, 128.1, 128.3, 134.2, 134.8, 135.6, 143.0, 146.3; HRMS (ESI): Calcd for C₂₀H₂₁O, [M-H]⁻ 277.1598. Found *m/z* 277.1603.

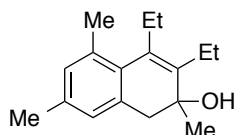
5b:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3477, 2964, 1441, 1373, 1059, 874, 743 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆): δ = 1.11–1.14 (m, 6H), 1.21 (t, *J* = 7.2 Hz, 3H), 2.40–2.64 (m, 4H), 2.75 (d, *J* = 14.8 Hz, 1H), 3.04 (d, *J* = 14.8 Hz, 1H), 3.71 (s, 1H), 7.08–7.16 (m, 2H), 7.20–7.24 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (100 MHz, acetone-d₆): δ = 14.2, 15.4, 20.7, 21.4, 25.8, 45.8, 72.6, 123.4, 126.2, 127.0, 128.4, 131.2, 135.3, 136.0, 145.6; HRMS (ESI): Calcd for C₁₅H₂₁O, [M+H]⁺ 217.1587. Found *m/z* 217.1586.

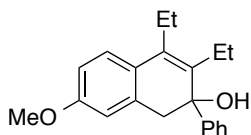
5c:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3476, 2970, 1452, 1144, 1063, 768 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆): δ = 1.18 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 2.46–2.76 (m, 4H),

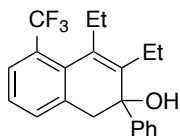
3.24 (dd, $J = 16.4, 0.8$ Hz, 1H), 3.30 (d, $J = 16.0$ Hz, 1H), 5.30 (s, 1H), 7.14–7.20 (m, 2H), 7.24–7.28 (m, 1H), 7.39 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, acetone- d_6): $\delta = 13.9, 15.6, 20.9, 21.7, 38.7, 74.3$ (q, $J = 27.1$ Hz), 123.8, 127.2, 127.3 (q, $J = 287.7$ Hz), 127.4, 127.6, 133.1, 134.5, 135.3, 138.5; HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{O}$, $[\text{M}-\text{H}]^-$ 269.1159. Found m/z 269.1163.

5d:

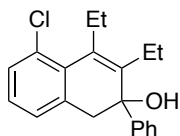
Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 10/1) as a pale yellow solid; IR (ATR): 3308, 2959, 1609, 1450, 1084, 824 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN): $\delta = 0.88$ (t, $J = 7.6$ Hz, 3H), 0.99 (s, 3H), 1.15 (t, $J = 7.6$ Hz, 3H), 2.24 (s, 3H), 2.32–2.54 (m, 6H), 2.59–2.73 (m, 3H), 2.82 (d, $J = 14.4$ Hz, 1H), 6.82 (d, $J = 0.8$ Hz, 1H), 6.84 (d, $J = 0.8$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 14.9, 15.9, 20.8, 21.1, 23.4, 23.6, 25.3, 47.5, 72.9, 127.5, 132.2, 133.1, 133.6, 133.8, 135.8, 137.7, 147.2$; HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{25}\text{O}$, $[\text{M}+\text{H}]^+$ 245.1900. Found m/z 245.1900.

5e:

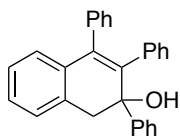
Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3477, 2961, 1607, 1499, 1252, 1136, 1030, 698 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): $\delta = 1.08$ (t, $J = 7.6$ Hz, 3H), 1.25 (t, $J = 7.6$ Hz, 3H), 2.18–2.27 (m, 1H), 2.41–2.50 (m, 1H), 2.62–2.80 (m, 2H), 3.08 (d, $J = 15.2$ Hz, 1H), 3.35 (d, $J = 15.2$ Hz, 1H), 3.74 (s, 3H), 4.26 (s, 1H), 6.57 (d, $J = 2.4$ Hz, 1H), 6.77 (dd, $J = 8.4, 2.8$ Hz, 1H), 7.13–7.23 (m, 3H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.42–7.46 (m, 2H); ^{13}C NMR (100 MHz, acetone- d_6): $\delta = 14.2, 15.1, 21.7, 21.8, 47.7, 55.0, 76.7, 111.7, 114.4, 124.6, 126.3, 127.0, 128.1, 128.5, 133.9, 136.5, 140.3, 146.6, 158.6$; HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2$, $[\text{M}+\text{H}]^+$ 309.1849. Found m/z 309.1838.

5f:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3422, 2964, 1697, 1447, 1306, 1115, 700 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): δ = 0.92 (t, J = 7.6 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 2.52–2.61 (m, 1H), 2.73–2.85 (m, 2H), 2.90–2.97 (m, 1H), 3.20 (d, J = 14.4 Hz, 1H), 3.30 (d, J = 14.8 Hz, 1H), 4.58 (s, 1H), 7.06–7.16 (m, 4H), 7.25 (d, J = 7.2 Hz, 1H), 7.39–7.42 (m, 2H), 7.47 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, acetone- d_6): δ = 14.80, 14.83, 21.9, 24.0 (q, J = 5.9 Hz), 47.7, 76.6, 124.9 (q, J = 30.1 Hz), 126.1 (q, J = 6.6 Hz), 126.2, 126.3 (q, J = 270.9 Hz), 127.2, 127.5, 128.0, 131.4, 135.3, 136.7, 138.1, 144.0, 147.3; HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{25}\text{F}_3\text{ON}$, $[\text{M}+\text{NH}_4]^+$ 364.1883. Found m/z 364.1874.

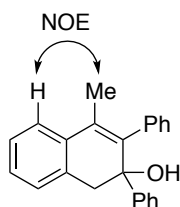
5g:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3454, 2964, 1697, 1443, 1252, 1038, 768, 698 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): δ = 1.10 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 2.45–2.54 (m, 1H), 2.65–2.74 (m, 1H), 2.84–2.93 (m, 1H), 3.15 (dd, J = 14.4, 1.2 Hz, 1H), 3.28–3.38 (m, 2H), 4.52 (s, 1H), 6.91–6.96 (m, 2H), 7.09–7.20 (m, 4H), 7.38–7.41 (m, 2H); ^{13}C NMR (100 MHz, acetone- d_6): δ = 14.4, 15.0, 22.0, 23.1, 47.8, 76.5, 126.9, 127.0, 127.37, 127.38, 128.1, 130.0, 130.1, 134.5, 134.6, 138.9, 144.3, 147.7; HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{21}\text{ClONa}$, $[\text{M}+\text{Na}]^+$ 335.1173. Found m/z 335.1163.

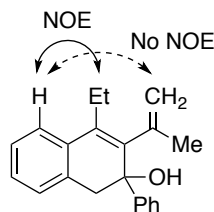
5h:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 10/1); IR (ATR): 3543, 2928, 1487, 1292, 1049, 700 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): δ = 3.39 (d, J = 15.6 Hz, 1H), 3.63 (d, J = 15.6 Hz, 1H), 4.38 (s, 1H), 6.71–6.73 (m, 1H),

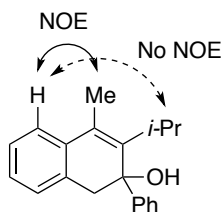
6.92–6.95 (m, 5H), 7.11–7.27 (m, 11H), 7.64–7.67 (m, 2H); ^{13}C NMR (100 MHz, acetone- d_6): δ = 47.9, 76.5, 126.3, 126.7, 126.9, 126.96, 127.01, 127.03, 127.3, 127.8, 128.2, 128.4, 128.5, 130.7, 131.3, 134.6, 136.9, 138.4, 139.5, 140.2, 143.3, 146.4; HRMS (ESI): Calcd for $\text{C}_{28}\text{H}_{23}\text{O}$, $[\text{M}+\text{H}]^+$ 375.1743. Found m/z 375.1731.

5i:

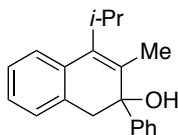
Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3449, 2922, 1487, 1011, 760, 698 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): δ = 2.03 (s, 3H), 3.27 (d, J = 15.6 Hz, 1H), 3.52 (d, J = 15.2 Hz, 1H), 4.04 (s, 1H), 7.07–7.32 (m, 11H), 7.46–7.52 (m, 3H); ^{13}C NMR (100 MHz, acetone- d_6): δ = 16.5, 47.5, 76.3, 124.3, 126.6, 126.9, 127.0, 127.3, 127.6, 128.00, 128.01, 128.4, 130.3, 130.5, 134.5, 136.2, 140.0, 142.8, 146.4; HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{21}\text{O}$, $[\text{M}+\text{H}]^+$ 313.1587. Found m/z 313.1571.

5j:

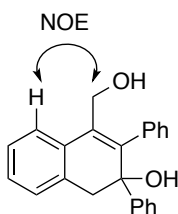
Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as pale yellow oil; IR (ATR): 3531, 2924, 1443, 1313, 1030, 779, 700 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): δ = 1.20 (t, J = 7.6 Hz, 3H), 1.74 (br s, 3H), 2.67–2.82 (m, 2H), 3.10 (d, J = 15.2 Hz, 1H), 3.37 (d, J = 15.2 Hz, 1H), 4.06 (s, 1H), 4.72 (br s, 1H), 5.01 (br s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.08–7.12 (m, 1H), 7.14–7.28 (m, 4H), 7.47–7.50 (m, 3H); ^{13}C NMR (100 MHz, acetone- d_6): δ = 14.7, 22.9, 24.7, 47.6, 75.6, 115.0, 124.3, 126.5 (2C), 127.0, 127.2 (2C), 127.9 (2C), 128.7, 134.4, 134.7, 135.1, 144.0, 144.4, 146.0; HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{23}\text{O}$, $[\text{M}+\text{H}]^+$ 291.1743. Found m/z 291.1730.

5k:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3447, 2959, 1447, 1015, 758, 700 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): δ = 1.21 (d, J = 7.2 Hz, 6H), 2.29 (s, 3H), 2.98–3.05 (m, 2H), 3.43 (d, J = 15.2 Hz, 1H), 4.32 (s, 1H), 6.90 (d, J = 7.2 Hz, 1H), 7.01–7.05 (m, 1H), 7.12–7.25 (m, 4H), 7.38–7.42 (m, 3H); ^{13}C NMR (100 MHz, acetone- d_6): δ = 16.0, 21.5, 22.5, 29.4, 48.2, 77.9, 123.2, 126.2, 126.6, 127.0, 127.2, 127.7, 128.0, 128.2, 133.7, 138.1, 146.4, 146.8; HRMS (EI): Calcd for $\text{C}_{20}\text{H}_{22}\text{O}$, $[\text{M}]^+$ 278.1671. Found m/z 278.1675.

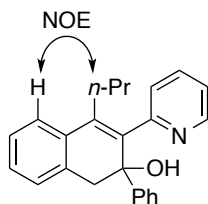
5l:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 5/1) as colorless oil; IR (ATR): 3406, 2957, 1682, 1447, 887, 762, 700 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): δ = 1.41 (d, J = 7.6 Hz, 3H), 1.50 (d, J = 7.2 Hz, 3H), 1.89 (s, 3H), 3.07 (d, J = 14.8 Hz, 1H), 3.27 (d, J = 14.8 Hz, 1H), 3.38 (sept, J = 7.6 Hz, 1H), 4.33 (s, 1H), 6.94–7.01 (m, 2H), 7.13–7.24 (m, 4H), 7.38–7.41 (m, 2H), 7.52 (d, J = 8.0 Hz, 1H), ^{13}C NMR (100 MHz, acetone- d_6): δ = 14.8, 20.6, 21.3, 29.8, 46.9, 76.9, 124.3, 126.1, 126.4, 126.6, 127.1, 128.2, 128.4, 134.8, 135.7, 137.90, 137.94, 145.6; HRMS (ESI): Calcd for $\text{C}_{20}\text{H}_{23}\text{O}$, $[\text{M}+\text{H}]^+$ 279.1743. Found m/z 279.1740.

5m:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 3/1) as a pale yellow solid; IR (ATR): 3288, 1489, 1024, 702 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): δ = 3.25 (d, J = 15.6 Hz, 1H), 3.54 (d, J = 15.6 Hz, 1H), 3.80 (t, J = 5.2 Hz,

1H), 4.07 (s, 1H), 4.41 (dd, $J = 11.6, 5.2$ Hz, 1H), 4.52 (dd, $J = 11.6, 5.2$ Hz, 1H), 7.06 (d, $J = 7.2$ Hz, 1H), 7.14–7.30 (m, 10H), 7.51–7.53 (m, 2H), 7.80 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, acetone- d_6): $\delta = 47.4, 59.9, 76.3, 125.7, 126.6$ (2C), 127.1, 127.2, 127.6, 127.9, 128.1 (2C), 128.4 (2C), 130.5, 134.5 (2C), 134.7, 134.9, 138.8, 144.8, 145.9; HRMS (ESI): Calcd for $\text{C}_{23}\text{H}_{21}\text{O}_2$, $[\text{M}+\text{H}]^+$ 329.1536. Found m/z 329.1530.

5n:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 4/1) as colorless oil; IR (ATR): 3368, 2957, 1701, 1587, 1464, 1244, 1040, 760, 702 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6): $\delta = 0.93$ (t, $J = 7.6$ Hz, 3H), 1.56–1.73 (m, 2H), 2.55–2.67 (m, 2H), 3.29 (d, $J = 16.0$ Hz, 1H), 3.34 (d, $J = 16.0$ Hz, 1H), 5.20 (br s, 1H), 7.03–7.08 (m, 1H), 7.12–7.17 (m, 4H), 7.21–7.25 (m, 1H), 7.30–7.33 (m, 2H), 7.48–7.51 (m, 2H), 7.59 (d, $J = 7.6$ Hz, 1H), 7.65–7.69 (m, 1H), 8.44 (dd, $J = 4.8, 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, acetone- d_6): $\delta = 14.2, 23.2, 31.5, 46.9, 76.6, 122.1, 124.8, 126.1, 126.6$ (3C), 127.2, 127.8, 128.2 (2C), 128.7, 133.9, 135.2, 136.3, 137.0, 139.4, 148.2, 148.8, 159.8; HRMS (ESI): Calcd for $\text{C}_{24}\text{H}_{24}\text{NO}$, $[\text{M}+\text{H}]^+$ 342.1852. Found m/z 342.1850.

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Chapter 3

Construction of Tetralin Skeltons Based on Rhodium-Catalyzed Site-Selective Ring Opening of Benzocyclobutenols

Abstract

An intermolecular reaction of benzocyclobutenols with electron-deficient alkenes provided tetrahydronaphthalene skeletons in the presence of a rhodium catalyst. A double bond of alkene was inserted into the proximal C(sp²)-C(sp³) bond selectively. The produced structures made a remarkable contrast with those synthesized from the identical starting materials under thermal reaction conditions.

Introduction

Tetralin is a key structural scaffold found in a wide variety of biologically active substances including natural products such as heritonine,¹ cycloolivil,² morphine,³ and daunorubicin.⁴ Much attention has been paid to develop synthetic strategy leading to tetralin skeletons. Herein is disclosed a new method to access tetralin derivatives from benzocyclobutenols based on their site-selective ring opening with the aid of a rhodium catalyst.^{5–8} 2-Hydroxytetralins are stereoselectively synthesized by an insertion reaction of vinyl ketones into the C(sp²)–C(sp³) bond of benzocyclobutenols. 2-Tetralones were also synthesized from 1-alkenylbenzocyclobutenols under the catalysis of rhodium. The produced structures make a remarkable contrast with those available from the identical starting materials under thermal reaction conditions.

A [4 + 2] cycloaddition reaction of *o*-quinodimethanes with alkenes presents one of the most reliable synthetic pathways to construct tetralin skeletons.⁹ For example, thermal reaction of benzocyclobutenols generates hydroxyl-substituted *o*-quinodimethanes¹⁰, which undergo regioselective [4 + 2] cycloaddition reaction with electron-deficient alkenes in an endo fashion.¹¹ It has also been known that treatment of benzocyclobutenols with butyllithium generates an oxyanion intermediate, which is an analogous pathway to form tetralin skeletons even at –78 °C.¹² In these cases, the C–C double bond is formally inserted into the C(sp³)–C(sp³) bond of the cyclobutene ring.

On the other hand, the author has shown a different type of ring opening reaction of benzocyclobutenols in chapter 2; a rhodium complex prompts the cleavage of the C(sp²)–C(sp³) bond to generate an *o*-acylmethyl-substituted arylrhodium intermediate.^{5,13,14} The subsequent intermolecular addition across the C–C triple bond of alkynes generates alkenylrhodium species, followed by intramolecular addition onto the carbonyl group to construct dihydronaphthalene frameworks. In a formal sense, a C–C triple bond is inserted into the C(sp²)–C(sp³) bond of the cyclobutene ring in an atom-economical manner. This outcome led the author to explore new synthetic pathways leading to tetralins (tetrahydronaphthalenes) from benzocyclobutenol derivatives.

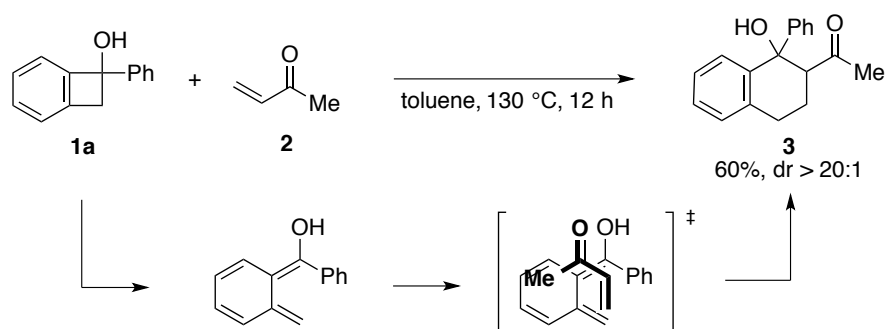
Results and Discussions

The author first carried out a thermal reaction of **1a** and **2a** at 100 °C for 30 min in the absence of a rhodium catalyst (Scheme 1a). The thermal ring opening reaction of **1a** was so slow that 90% of **1a** was recovered. Next tried was the reaction of **1a** and **2a** in

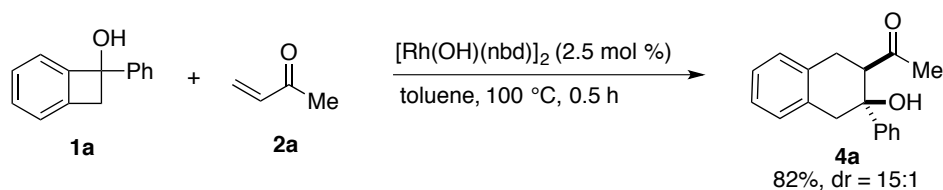
the presence of $[\text{Rh}(\text{OH})(\text{nbd})]_2$ under otherwise identical conditions. The C–C double bond of **2a** was successfully inserted into the $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^3)$ bond of **1a** to produce 2-hydroxytetralin **4a** in 82% yield with a trace amount of the minor diastereomer (diastereomeric ratio, dr = 15:1) (Scheme 1b).

Scheme 1. Thermal reaction vs. Rhodium-catalyzed reaction

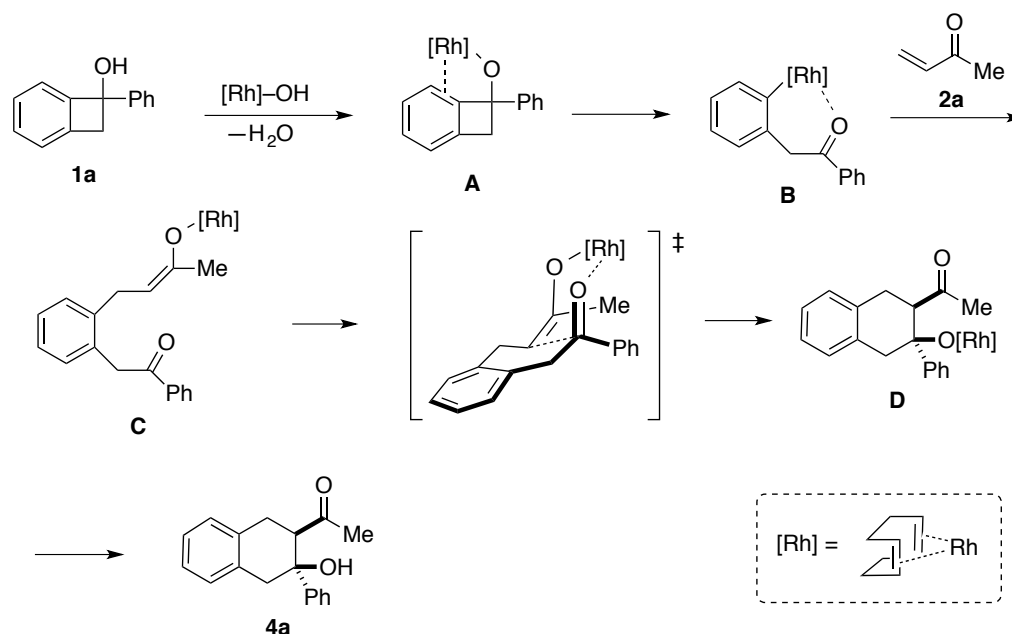
(a) Thermal reaction



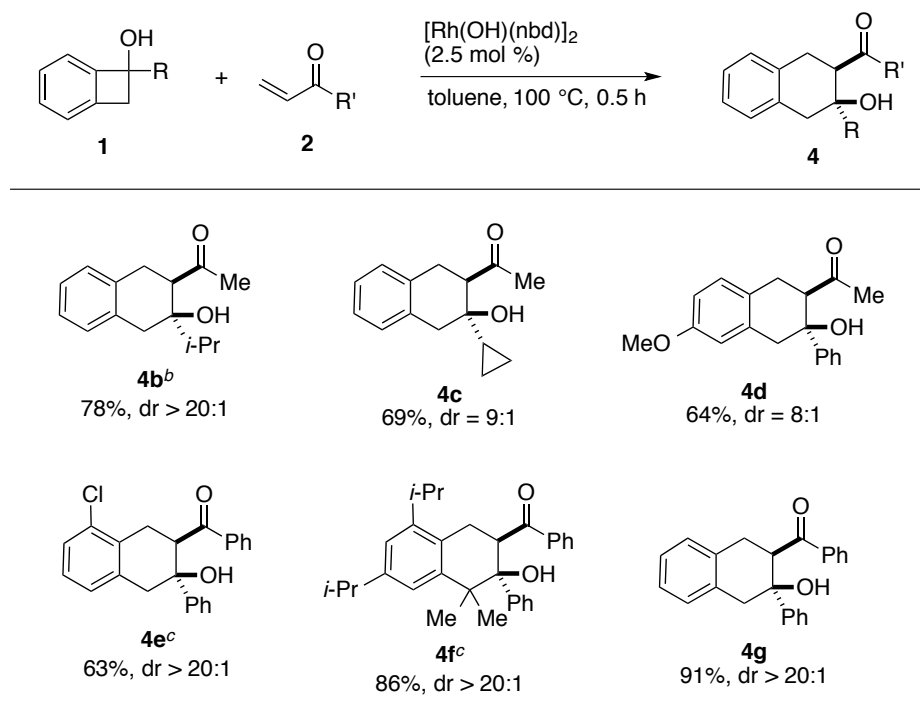
(b) Rhodium-catalyzed reaction



A feasible mechanistic scenario for the diastereoselective formation of **4a** is depicted in Scheme 2. Initially, the hydroxylic proton of benzocyclobutenol **1a** is exchanged with rhodium to furnish the rhodium benzocyclobutenolate **A**. The benzene ring π -coordinates to the rhodium center.¹⁵ This π -coordination is retained during the subsequent β -carbon elimination so that the ipso carbon selectively migrates onto rhodium. Thus, the $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^3)$ bond is selectively cleaved. The resulting arylrhodium species **B** undergoes conjugate addition across **2a**, which is taking an *s-cis* conformation to allow a six-membered transition state. As a consequence, the (*Z*)-enolate **C** is generated. Then, an intramolecular aldol reaction takes place again via a six-membered transition state, for which chair-like transition state is assumed, to afford syn-aldolate **D** with stereoselectivity.^{16,17} Protonation of **D** with water, generated in the first step, or with **1a** produces **4a** and the next catalytic cycle restarts.

Scheme 2. Proposed mechanism for the formation of **4a**

The scope of the site-selective insertion reaction is shown in Table 1. Although non-substituted benzocyclobutenol ($R = H$) failed to afford the 2-hydroxytetralin, substituted benzocyclobutenols reacted with vinyl ketones to afford **4b–g** with dr ranging from 8:1 to >20:1. Cyclopropyl, methoxy and chloro groups remained intact under the reaction conditions. The site-selective ring opening was observed even when the migrating ipso carbon was hindered due to its *ortho*-isopropyl group. Phenyl vinyl ketone was also successfully engaged in the insertion reaction. On the other hand, alkenes lacking electron-withdrawing groups (e.g. ethylene and styrene) were not applicable for this reaction. α,β -Unsaturated ketones possessing a substituent at the α - or β -position gave significantly lower yield, presumably due to steric reasons. The use of acrolein and acrylate gave a complex mixture containing the desired 2-hydroxytetralin (<30% yield).

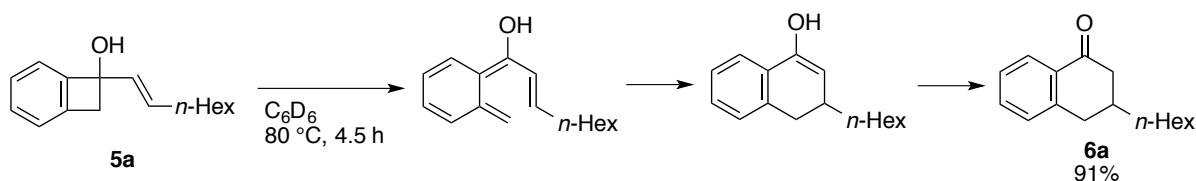
Table 1. Rhodium-catalyzed reactions of **1** and **2**

^a Reaction conditions: benzocyclobutenol **1** (0.20 mmol), vinyl ketone **2** (0.40 mmol, 2 equiv.), $[\text{Rh}(\text{OH})(\text{nbd})]_2$ (2.5 mol %), toluene (1 mL), 100 °C, 0.5 h. Isolated yields of the major diastereomer were shown. dr were determined by NMR analysis of the crude reaction mixture. ^b 1 h. ^c $[\text{Rh}(\text{OH})(\text{cod})]_2$ (2.5 mol %) was employed as the catalyst.

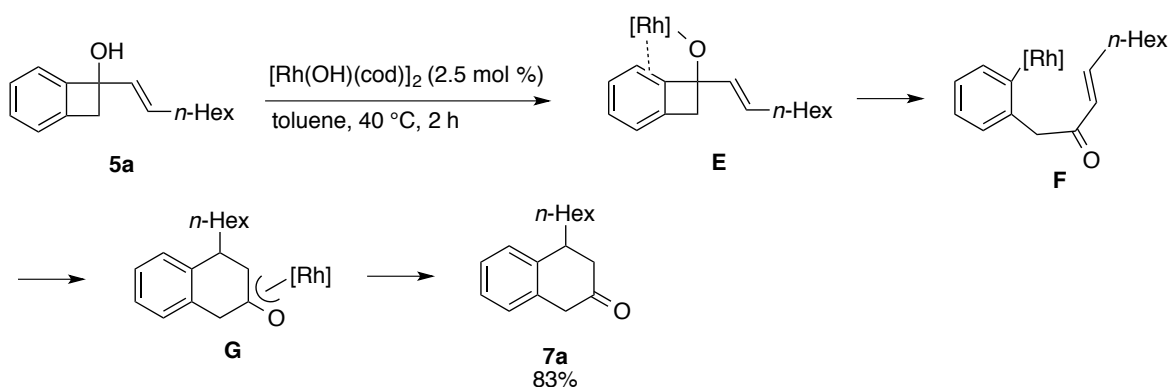
Next examined was the construction of tetralones from 1-alkenylbenzocyclobutenol **5a**, which was easily prepared by addition of alkenyllithium to benzocyclobutenone. When **5a** was simply heated at 80 °C in C_6D_6 for 4.5 h, 1-tetralone **6a** was obtained in 91% yield, as previously reported for analogous substrates (Scheme 3a).¹⁸ 4 π -Electrocyclic ring opening of **5a** is followed by 6 π -electrocyclic ring closure to afford **6a**. In sharp contrast, treatment of **5a** with a catalytic amount of $[\text{Rh}(\text{OH})(\text{cod})]_2$ at 40 °C for 2 h gave 2-tetralone **7a** in 83% isolated yield.¹⁹ Mechanistically, it is assumed that the site-selective cleavage of the $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bond generates the arylrhodium intermediate **F** with the *ortho* position substituted by an α,β -unsaturated carbonyl group. An intramolecular conjugate addition reaction occurs and the resulting oxa- π -allylrhodium **G** is protonated with water, or with **5a** to give **7a** (Scheme 3b).

Scheme 3. Thermal reaction vs. Rhodium-catalyzed reaction

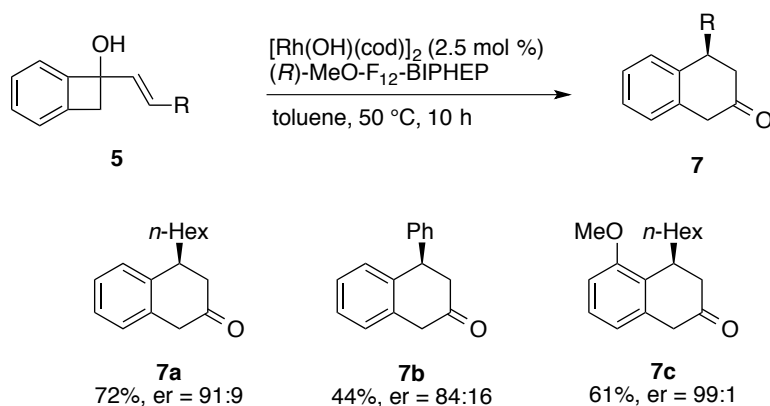
(a) Thermal reaction



(b) Rhodium-catalyzed reaction



Thus, a rhodium complex also changes the pathway of the intramolecular rearrangement reaction of **5a**. In addition, the racemic mixture of **5a** was enantioselectively rearranged when electron-deficient chiral diposphine (*R*)-MeO- F_{12} -BIPHEP²⁰ was employed as the ligand for rhodium. 2-Tetralone **7a** was obtained in 72% yield with the enantiomeric ratio (er) of 91:9. This reaction condition was applied to the synthesis of **7b** (er = 84:16) and **7c** (er = 99:1) (Scheme 4).

Scheme 4. Asymmetric rearrangement of **5**

Conclusions

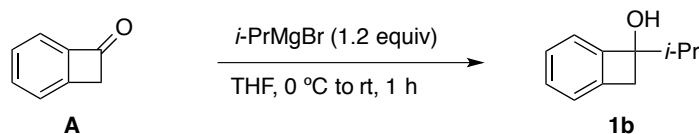
Tetralin skeletons are constructed from benzocyclobutenols based on the rhodium-catalyzed site-selective ring opening reaction. Vinyl ketones are site-selectively inserted into the C(sp²)-C(sp³) bond of benzocyclobutenols to produce 2-hydroxytetralins. 1-Alkenylbenzocyclobutenols are restructured into 2-tetralones via intramolecular conjugate addition. The obtained tetralins markedly contrast with those given by the conventional thermal reactions.

Experimental section

General. All reactions were carried out under an argon atmosphere in an oven-dried glassware with standard Schlenk techniques. Photoreactions were conducted with Rayonet RPR-100. IR measurements were performed on a FTIR SHIMADZU DR-8000. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-vx400 (^1H at 400.44 MHz and ^{13}C at 100.69 MHz) and JEOL JNM-ECA600 (^1H at 600.17 MHz) spectrometer. NMR data were obtained in CDCl_3 or C_6D_6 . Proton chemical shifts were referenced to the residual proton signal of the solvent at 7.26 ppm (CHCl_3), 7.16 ppm (C_6H_6). Carbon chemical shifts were referenced to the carbon signal of the solvent at 77.0 ppm (CDCl_3) and 128.62 ppm (C_6D_6). High-resolution mass spectra were recorded on a Thermo Scientific Exactive (ESI, APCI, EI). Flash column chromatography was performed with silica gel 60N (Kanto). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck). HPLC analysis was performed by 4.6×250 mm column. Gel permeation chromatography was carried out with a Japan Analytical Industry LC-908.

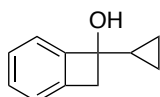
Materials. Toluene was distilled over sodium/benzophenone ketyl. $[\text{Rh}(\text{OH})(\text{cod})]_2$,^{21a} $[\text{Rh}(\text{OH})(\text{nbd})]_2$,^{21a} benzocyclobutenol **1a**,^{21b} benzocyclobutenol **1d**,^{5a} benzocyclobutenol **1e**,^{5a} benzocyclobutenol **1f**,^{21c} and (*E*)-1-iodo-1-octene^{21d} were prepared according to the literature procedures. All other chemicals were available from commercial sources and were used as received without further purification.

A procedure for the synthesis of benzocyclobutenols (**1b**, **1c**)

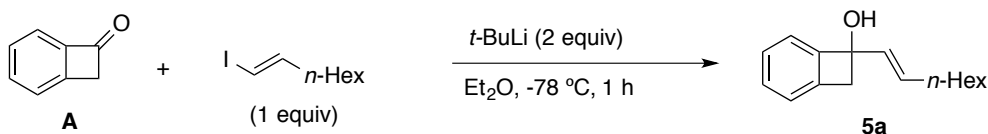


To a solution of benzocyclobutenone **A** (354 mg, 3.0 mmol) in THF (10 mL), a solution of *i*-PrMgBr in THF (3.0 M, 2.5 mL, 0.84 mmol) was added dropwise at 0 °C. Then, the reaction mixture was warmed to room temperature. The resulting mixture was quenched by addition of a saturated NH_4Cl solution and the aqueous solution was extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, and then was dried over Na_2SO_4 . The solvent was removed by reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) and gel permeation chromatography to give benzocyclobutenol **1b** (203 mg, 1.3

mmol, 42%) as colorless oil; IR (ATR): 3383, 2961, 1456, 1364, 752, 716 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.04 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H), 1.82–2.08 (m, 2H), 3.06 (d, J = 14.4 Hz, 1H), 3.39 (d, J = 14.0 Hz, 1H), 7.15–7.30 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ = 17.2, 17.3, 35.3, 44.9, 83.9, 121.5, 123.8, 126.9, 129.1, 141.9, 149.8; HRMS (APCI): Calcd for $\text{C}_{11}\text{H}_{15}\text{O}$, $[\text{M}+\text{H}]^+$ 163.1117. Found m/z 163.1115.

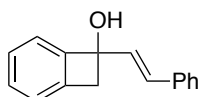
1c:

According to the procedure analogous to that described for **1b**, **1c** (81 mg, 0.5 mmol, 24%) was prepared from benzocyclobutenone (244 mg, 2.1 mmol). Purified by gel permeation chromatography after column chromatography on silica gel (hexane/ethyl acetate = 3/1) afforded **1c** as white solid; IR (ATR): 3207, 3007, 1456, 1352 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = -0.02–0.04 (m, 1H), 0.43–0.61 (m, 3H), 1.41–1.48 (m, 1H), 2.06 (s, 1H), 3.19 (d, J = 14.0 Hz, 1H), 3.39 (d, J = 14.0 Hz, 1H), 7.08–7.29 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ = 9.1, 31.8, 46.4, 81.4, 121.1, 123.9, 127.1, 129.2, 141.5, 150.2; HRMS (APCI): Calcd for $\text{C}_{11}\text{H}_{13}\text{O}$, $[\text{M}+\text{H}]^+$ 161.0961. Found m/z 161.0959.

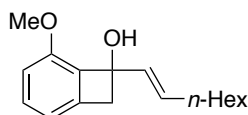
A procedure for the synthesis of 1-alkenylbenzocyclobutenols (5a, 5b, 5c)

To a solution of (*E*)-1-iodo-1-octene (7.14 g, 30 mmol) in Et_2O (40 mL), *t*-BuLi (1.67 M, 37.5 mL, 60 mmol) was added dropwise at $-78\text{ }^\circ\text{C}$. After 0.5 h, the reaction mixture was warmed to room temperature for 1 h. The reaction mixture was cooled to $-78\text{ }^\circ\text{C}$. Then, benzocyclobutenone (3.54 g, 30 mmol) was added dropwise. After 1 h, the resulting mixture was quenched by addition of HCl (2.0 M) at $-78\text{ }^\circ\text{C}$ and the aqueous solution was extracted with Et_2O . The combined organic layer was washed with a saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution and brine, and then was dried over Na_2SO_4 . The solvent was removed by reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) and gel permeation chromatography to give benzocyclobutenol **5a** (3.7 g, 16 mmol, 54%) as colorless oil; IR (ATR): 3321, 2922,

2853, 1456 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 0.87 (t, J = 6.8 Hz, 3H), 1.21–1.39 (m, 8H), 2.00–2.13 (m, 2H), 2.30 (s, 1H), 3.31 (d, J = 14.4 Hz, 1H), 3.45 (d, J = 14.0 Hz, 1H), 5.78 (dt, J = 15.2, 6.4 Hz, 1H), 5.87 (d, J = 15.6 Hz, 1H), 7.17–7.32 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ = 14.1, 22.6, 28.9, 29.1, 31.7, 32.1, 48.1, 80.1, 121.3, 124.1, 127.3, 129.4, 130.7, 131.6, 141.7, 149.1; HRMS (EI): Calcd for $\text{C}_{16}\text{H}_{23}\text{O}$, $[\text{M}+\text{H}]^+$ 231.1743. Found m/z 231.1740.

5b:

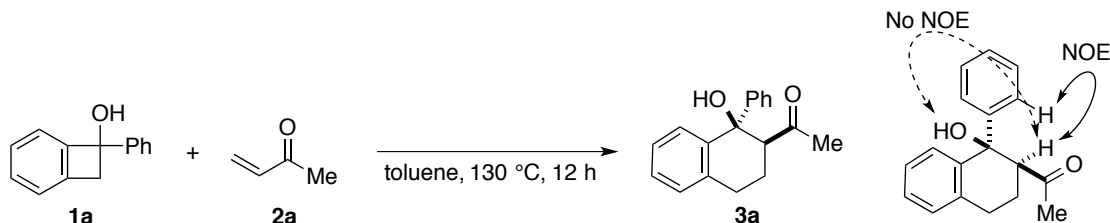
According to the procedure analogous to that described for **5a**, **5b** (0.59 g, 2.6 mmol, 26%) was prepared from benzocyclobutenone (1.18 g, 10 mmol). Purified by column chromatography on silica gel (hexane/ethyl acetate = 7/1) and gel permeation chromatography to give benzocyclobutenol **5b** as white solid; IR (ATR): 3314, 1668, 1599, 1495 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.45 (s, 1H), 3.42 (d, J = 14.0 Hz, 1H), 3.58 (d, J = 14.4 Hz, 1H), 6.57 (d, J = 16.0 Hz, 1H), 6.74 (d, J = 16.0 Hz, 1H), 7.22–7.40 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ = 48.5, 80.2, 121.5, 124.2, 126.6, 127.56, 127.60, 128.5, 128.7, 129.7, 131.5, 136.6, 141.6, 148.8; HRMS (ESI): Calcd for $\text{C}_{16}\text{H}_{15}\text{O}$, $[\text{M}+\text{H}]^+$ 223.1117. Found m/z 223.1114.

5c:

According to the procedure analogous to that described for **5a**, **5c** (587 mg, 2.3 mmol, 46%) was prepared from 2-methoxybenzocyclobutenone (740 mg, 5.0 mmol). Purified by column chromatography (hexane/ethyl acetate = 7/1) and gel permeation chromatography to give benzocyclobutenol **5c** as colorless oil; IR (ATR): 3418, 2924, 1603, 1580 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 0.88 (t, J = 6.8 Hz, 3H), 1.24–1.39 (m, 8H), 2.03–2.09 (m, 2H), 2.54 (s, 1H), 3.25 (d, J = 14.0 Hz, 1H), 3.39 (d, J = 14.0 Hz, 1H), 3.88 (s, 3H), 5.79 (dt, J = 15.6, 6.0 Hz, 1H), 5.86 (d, J = 15.6 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 7.2 Hz, 1H), 7.22 (dd, J = 8.4, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 14.1, 22.6, 28.9, 29.1, 31.7, 32.1, 48.4, 57.3, 79.6, 113.7, 116.1, 130.0, 131.1, 132.8, 132.9, 143.2, 154.0; HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{25}\text{O}_2$, $[\text{M}+\text{H}]^+$

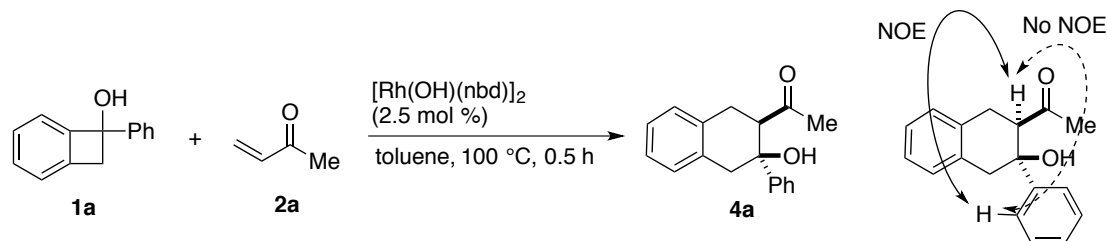
261.1849. Found m/z 261.1844.

A procedure for thermal reaction of benzocyclobutenol **1a** and **2a**



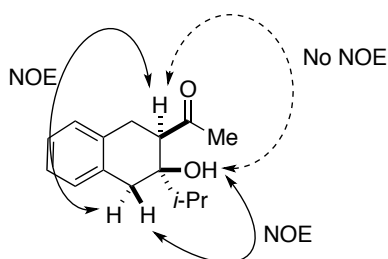
A solution of benzocyclobutenol **1a** (39.2 mg, 0.20 mmol) and methyl vinyl ketone **2a** (32.6 μ L, 0.40 mmol, 2 equiv) in toluene (1 mL) was stirred at 130 °C for 12 h. After the reaction mixture was cooled to room temperature, concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 10/1) to give tetralin **3a** (31.9 mg, 0.12 mmol, 60%); IR (ATR): 3437, 1697, 1447, 1198 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.95–2.07 (m, 4H), 2.31–2.42 (m, 1H), 3.00–3.04 (m, 2H), 3.36 (dd, J = 11.2, 2.8 Hz, 1H), 4.83 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.13–7.36 (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ = 22.4, 28.9, 31.0, 58.3, 75.8, 126.51, 126.53, 126.9, 127.5, 127.9, 128.5, 129.4, 135.4, 140.9, 146.8, 214.3; HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{Na}$, $[\text{M}+\text{Na}]^+$ 289.1199. Found m/z 289.1189.

A typical procedure for rhodium-catalyzed reactions

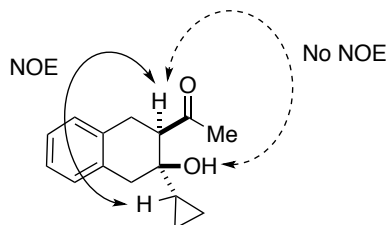


To an oven-dried flask equipped with a stirrer bar were added $[\text{Rh}(\text{OH})(\text{nbd})]_2$ (5.0 μ mol, 2.5 mol %) and benzocyclobutenol **1a** (39.3 mg, 0.20 mmol, 1.0 equiv). The flask was capped with a rubber septum, evacuated and refilled with argon three times. Then, a solution of methyl vinyl ketone **2a** (32.6 μ L, 0.40 mmol, 2.0 equiv) in dry toluene (1 mL) was added by syringe. After being stirred at 100 °C for 30 min, the reaction mixture was cooled to room temperature. The resulting mixture was passed through a pad of Florisil[®] and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on

silica gel (hexane/ethyl acetate = 7/1) to give tetralin **4a** as yellow solid (43.5 mg, 0.16 mmol, 82%); IR (ATR): 3474, 1695, 1167, 1067 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 2.04 (s, 3H), 3.00–3.05 (m, 2H), 3.17 (d, J = 17.4 Hz, 1H), 3.27 (dd, J = 16.2, 12.6 Hz, 1H), 3.65 (dd, J = 12.6, 4.8 Hz, 1H), 4.21 (d, J = 2.4 Hz, 1H), 7.07–7.08 (m, 1H), 7.16–7.17 (m, 3H), 7.27 (t, J = 7.8 Hz, 1H), 7.36–7.39 (m, 2H), 7.50–7.52 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 30.0, 31.8, 44.2, 53.3, 73.7, 124.7, 126.0, 126.4, 127.1, 128.2, 128.5, 129.2, 133.3, 134.0, 146.8, 214.7; HRMS (APCI): Calcd for $\text{C}_{18}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 267.1380. Found m/z 267.1373.

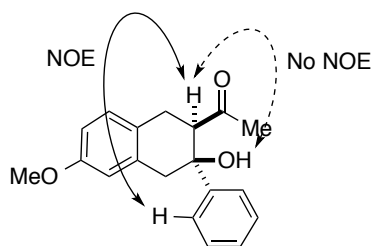
4b:

Purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 7/1); IR (ATR): 3501, 2961, 1692, 1169 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 0.90 (d, J = 7.2 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H), 1.94–1.99 (m, 1H), 2.38 (s, 3H), 2.70 (d, J = 17.4 Hz, 1H), 2.77 (d, J = 17.4 Hz, 1H), 2.92 (dd, J = 15.6, 4.2 Hz, 1H), 3.06–3.11 (m, 1H), 3.18 (dd, J = 12.6, 6.6 Hz, 1H), 3.58 (d, J = 1.8 Hz, 1H), 7.11–7.18 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ = 16.4, 18.3, 30.4, 31.1, 33.4, 35.9, 51.2, 74.6, 125.6, 126.3, 127.9, 129.7, 133.7, 134.1, 215.3; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{21}\text{O}_2$, $[\text{M}+\text{H}]^+$ 233.1536. Found m/z 233.1529.

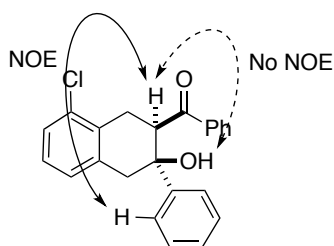
4c:

Purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 7/1); IR (ATR): 3503, 1693, 1364, 752 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6): δ = 0.13–0.20 (m, 2H), 0.36–0.39 (m, 1H), 0.42–0.45 (m, 1H), 0.58–0.60 (m, 1H), 1.81 (s, 3H), 2.34–2.42 (m, 2H), 2.55 (d, J = 16.8 Hz, 1H), 2.83 (d, J = 16.8 Hz, 1H), 3.09 (dd, J =

15.6, 12.0 Hz, 1H), 3.26 (d, $J = 1.8$ Hz, 1H), 6.91–6.93 (m, 1H), 6.96–6.97 (m, 1H), 7.04–7.09 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = -0.1, 2.1, 21.1, 30.6, 32.7, 42.4, 54.3, 69.8, 126.5, 127.0, 129.1, 130.1, 134.9, 135.3, 214.9$; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 231.1380. Found m/z 231.1375.

4d:

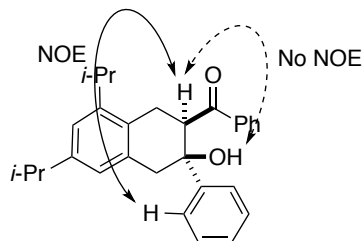
Purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 7/1); IR (ATR): 3485, 1699, 1611, 1504 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6): $\delta = 1.50$ (s, 3H), 2.46 (dd, $J = 16.2, 5.4$ Hz, 1H), 2.80 (d, $J = 17.4$ Hz, 1H), 2.89–2.93 (m, 2H), 3.10 (dd, $J = 15.6, 12.0$ Hz, 1H), 3.37 (s, 3H), 4.44 (d, $J = 3.0$ Hz, 1H), 6.52 (d, $J = 1.8$ Hz, 1H), 6.81 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 7.07 (t, $J = 7.2$ Hz, 1H), 7.16–7.19 (m, 2H), 7.36–7.38 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 30.2, 31.9, 45.6, 53.9, 55.4, 74.5, 113.4, 114.4, 125.8, 126.7, 127.6, 129.1, 130.0, 136.8, 148.6, 159.3, 214.6$; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{21}\text{O}_3$, $[\text{M}+\text{H}]^+$ 297.1485. Found m/z 297.1479.

4e:

Purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 7/1); IR (ATR): 3429, 1651, 1595, 1213 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6): $\delta = 2.91$ (d, $J = 17.6$ Hz, 1H), 3.03 (d, $J = 17.2$ Hz, 1H), 3.28–3.37 (m, 2H), 4.06 (dd, $J = 10.4, 8.0$ Hz, 1H), 5.02 (d, $J = 2.8$ Hz, 1H), 6.72 (d, $J = 7.6$ Hz, 1H), 6.81 (t, $J = 8.0$ Hz, 1H), 6.89–6.95 (m, 3H), 7.01–7.06 (m, 3H), 7.14–7.16 (m, 1H), 7.44–7.46 (m, 2H), 7.55–7.57 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 29.7, 45.1, 46.8, 73.8, 124.6, 126.8, 127.0, 127.2, 127.7, 128.2, 128.4, 128.9, 131.8, 133.7, 134.0, 136.1, 136.6, 146.6,$

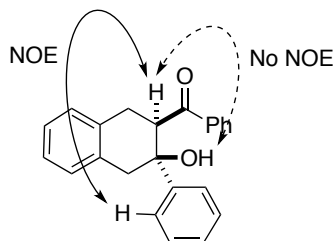
205.6; HRMS (APCI): Calcd for $C_{23}H_{20}O_2Cl$, $[M+H]^+$ 363.1146. Found m/z 363.1136.

4f:



Purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 7/1); IR (ATR): 3422, 2961, 1657, 1447 cm^{-1} ; 1H NMR (400 MHz, C_6D_6): δ = 1.05 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.25 (s, 3H), 1.28 (d, J = 2.0 Hz, 3H), 1.29 (d, J = 2.0 Hz, 3H), 1.61 (s, 3H), 2.82–2.92 (m, 2H), 3.22 (dd, J = 16.0, 5.2 Hz, 1H), 3.44 (dd, J = 16.4, 12.4 Hz, 1H), 4.89 (dd, J = 12.4, 5.2 Hz, 1H), 4.98 (s, 1H), 6.75 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 7.00–7.04 (m, 3H), 7.09–7.16 (m, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.84–7.86 (m, 2H), 8.14 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 23.6, 24.28, 24.34, 25.10, 25.14, 29.4, 30.2, 32.7, 35.4, 44.3, 45.0, 79.7, 120.9, 124.3, 127.4, 127.5, 127.6, 129.0, 129.7, 130.1, 134.3, 137.8, 145.97, 146.04, 146.2, 147.5, 207.1; HRMS (APCI): Calcd for $C_{31}H_{37}O_2$, $[M+H]^+$ 441.2788. Found m/z 441.2778.

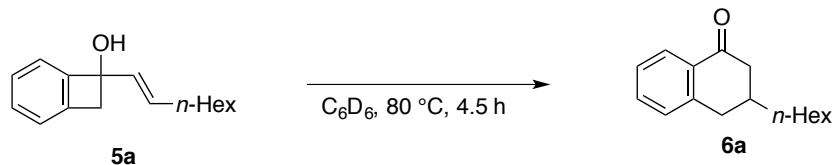
4g:



Purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 7/1) as white solid; IR (ATR): 3464, 3024, 2363, 1651, 1661 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$): δ = 3.11–3.18 (m, 2H), 3.25 (d, J = 17.4 Hz, 1H), 3.45 (dd, J = 15.6, 12.6 Hz, 1H), 4.58 (dd, J = 13.2, 5.4 Hz, 1H), 4.80 (d, J = 2.4 Hz, 1H), 7.13–7.22 (m, 5H), 7.26–7.29 (m, 2H), 7.47 (t, J = 7.8 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.92 (d, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.6, 45.0, 47.2, 74.2, 124.6, 125.9, 126.4, 126.8, 128.16, 128.18, 128.3, 128.8, 129.2, 133.6, 133.9, 134.3, 136.1, 147.2, 205.7; HRMS (APCI): Calcd for $C_{23}H_{21}O_2$, $[M+H]^+$ 329.1536.

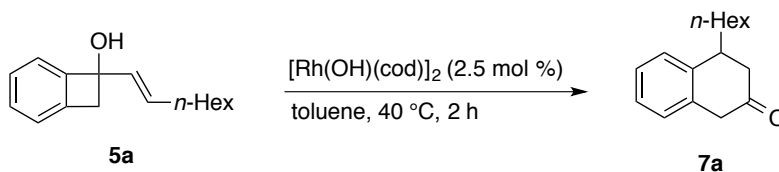
Found m/z 329.1527.

A procedure for thermal rearrangement of benzocyclobutenol **5a**



A solution of benzocyclobutenol **5a** (33.2 mg, 0.14 mmol) in C_6D_6 (1 mL) was heated at 80 °C for 4.5 h. After the reaction mixture was cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 10/1) to give 1-tetralone **6a** (30.3 mg, 0.127 mmol, 91%); IR (ATR): 2924, 2855, 1682, 1601 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 0.89 (t, J = 6.8 Hz, 3H), 1.29–1.47 (m, 10H), 2.14–2.24 (m, 1H), 2.31 (dd, J = 16.0, 12.0 Hz, 1H), 2.69 (dd, J = 16.4, 10.8 Hz, 1H), 2.77 (ddd, J = 16.4, 3.2, 2.0 Hz, 1H), 3.00 (ddd, J = 16.0, 3.6, 1.6 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.30 (pseudo t, J = 7.2 Hz, 1H), 7.47 (pseudo td, J = 7.6, 1.6 Hz, 1H), 8.01 (dd, J = 8.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 14.1, 22.6, 26.5, 29.3, 31.8, 35.4, 35.8, 36.2, 45.5, 126.6, 127.0, 128.9, 132.5, 133.5, 143.8, 198.6; HRMS (ESI): Calcd for $\text{C}_{16}\text{H}_{23}\text{O}$, $[\text{M}+\text{H}]^+$ 231.1743. Found m/z 231.1741.

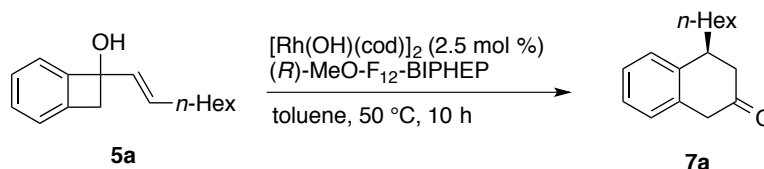
A typical procedure for rhodium-catalyzed rearrangement



To an oven-dried vial equipped with a stirrer bar was added $[\text{Rh}(\text{OH})(\text{cod})]_2$ (2.2 mg, 5.0 μmol , 2.5 mol %). The vial was purged with nitrogen gas. Then, a solution of **5a** (46.0 mg, 0.20 mmol) in dry toluene (0.8 mL) was added and heated at 40 °C for 2 h. The reaction mixture was then cooled to room temperature. The resulting mixture was passed through a pad of Florisil[®] and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 11/1) to give 2-tetralone **7a** as yellow oil (38.4 mg, 0.17 mmol, 83%); IR (ATR): 2924, 2855, 1717, 1456 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 0.87 (t, J = 6.8 Hz, 3H), 1.26–1.65 (m, 10H), 2.54 (dd, J

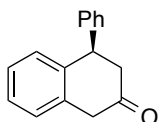
= 16.4, 4.4 Hz, 1H), 2.69 (dd, J = 16.4, 5.6 Hz, 1H), 3.05–3.12 (m, 1H), 3.60 (s, 2H), 7.11–7.13 (m, 1H), 7.19–7.23 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 14.0, 22.6, 27.3, 29.2, 31.7, 35.0, 39.6, 43.8, 44.2, 126.6, 126.7, 127.7, 128.7, 132.7, 140.2, 210.6; HRMS (EI): Calcd for $\text{C}_{16}\text{H}_{22}\text{O}$, $[\text{M}]^+$ 230.1671. Found m/z 230.1670.

A typical procedure for rhodium-catalyzed asymmetric rearrangement



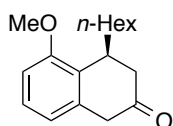
To an oven-dried vial equipped with a stirrer bar were added $[\text{Rh}(\text{OH})(\text{cod})]_2$ (2.2 mg, 5.0 μmol , 2.5 mol %) and (*R*)-MeO-F₁₂-BIPHEP (9.6 mg, 12.0 μmol , 6.0 mol %). The vial was purged with nitrogen gas. Then, toluene (0.5 mL) was added and the reaction mixture was stirred at room temperature for 12 h. A solution of **5a** (46.0 mg, 0.20 mmol) in dry toluene (0.5 mL) was added and the reaction mixture was stirred at 50 $^\circ\text{C}$ for 10 h. The reaction mixture was then cooled to room temperature. The resulting mixture was passed through a pad of Florisil[®] and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 14/1) to give (–)-2-tetralone **7a** as yellow oil (37.6 mg, 0.16 mmol, 82%, er = 91:9 (Daicel CHIRALPAK IB column, hexane/*i*-PrOH = 99.5/0.5, 0.67 mL/min, retention times: t_1 = 7.95 min, t_2 = 8.71 min), $[\alpha]_D^{23}$ = –45.6 (c = 2.6×10^{-2} M in CHCl_3)). The absolute stereochemistry was assigned by analogy of **7b**.

7b:



Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 15/1) to afford **7b** as yellow oil (19.5 mg, 0.09 mmol, 44%, er = 16:84 (Daicel CHIRALPAK IB column, hexane/*i*-PrOH = 99.5/0.5, 0.67 mL/min, retention times: t_1 = 19.53 min, t_2 = 26.26 min), $[\alpha]_D^{25}$ = +5.17 (c = 1.8×10^{-2} M in CHCl_3)); IR(ATR): 3026, 1713, 1601, 1495 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.90 (dd, J = 16.8, 6.0 Hz, 1H), 2.95 (dd, J = 16.4, 7.2 Hz, 1H), 3.60 (d, J = 20.0 Hz, 1H), 3.68 (d, J = 20.0 Hz, 1H), 4.47 (pseudo t,

$J = 6.4$ Hz, 1H), 7.01 (d, $J = 7.6$ Hz, 1H), 7.14 (d, $J = 7.6$ Hz, 2H), 7.18–7.22 (m, 2H), 7.24–7.28 (m, 2H), 7.32–7.36 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 44.6, 44.9, 45.7, 126.97, 126.98, 127.3, 127.9, 128.1, 128.5, 128.8, 133.3, 139.3, 141.4, 209.4$; HRMS (EI): Calcd for $\text{C}_{16}\text{H}_{14}\text{O}$, $[\text{M}]^+$ 222.1045. Found m/z 222.1048. The absolute stereochemistry was assigned by comparison of the optical rotation with the reported data.²²

7c:

Purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 13/1) to afford **7c** as yellow oil (31.5 mg, 0.12 mmol, 61%, er = 99:1 ((Daicel CHIRALPAK IB column, hexane/*i*-PrOH = 99.5/0.5, 0.67 mL/min, retention times: $t_1 = 8.65$ min, $t_2 = 11.38$ min), $[\alpha]_D^{23} = -113.1$ ($c = 1.7 \times 10^{-2}$ M in CHCl_3)); IR (ATR): 2926, 2855, 1717, 1585 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): $\delta = 0.87$ (t, $J = 6.8$ Hz, 3H), 1.18–1.51 (m, 10H), 2.54 (dd, $J = 16.0, 6.8$ Hz, 1H), 2.67 (dd, $J = 16.0, 2.4$ Hz, 1H), 3.57 (s, 2H), 3.59–3.65 (m, 1H), 3.84 (s, 3H), 6.71 (d, $J = 7.6$ Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 7.17 (pseudo t, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.1, 22.6, 27.1, 29.1, 31.7, 32.4, 34.5, 43.1, 43.5, 55.3, 108.4, 120.8, 127.4, 129.2, 134.2, 156.5, 211.1$; HRMS (EI): Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_2$, $[\text{M}]^+$ 260.1776. Found m/z 260.1772. The absolute stereochemistry was assigned by analogy of **7b**.

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Chapter 4

Stereospecific Construction of Planar Chirality through Carbon–Carbon Bond Cleavage

Abstract

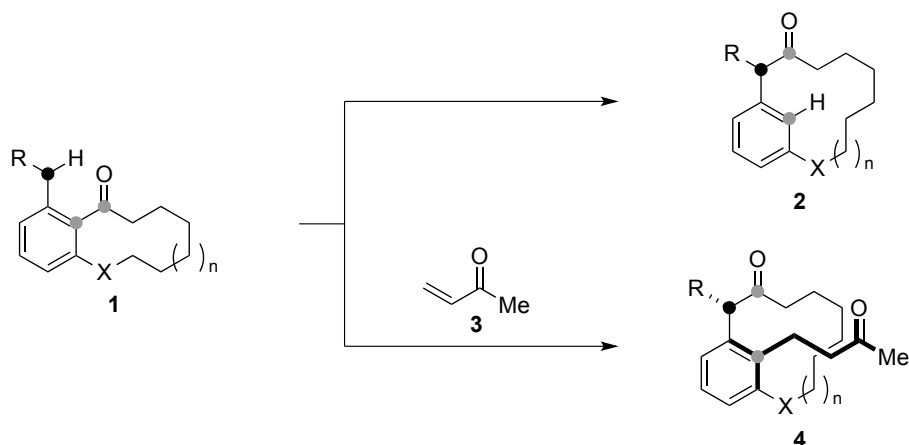
A tricyclic benzocyclobutenol with central chirality was reacted with methyl vinyl ketone in the presence of a rhodium catalyst. The cyclobutene ring was opened by β -carbon elimination and the resulting arylrhodium species underwent conjugate addition to methyl vinyl ketone leading to a metacyclophane with planar chirality. In this reaction, central chirality is transferred to planar chirality in a stereospecific manner during the process of the carbon–carbon bond cleavage by β -carbon elimination.

Introduction

Metacyclophanes are cyclic compounds possessing a central arene moiety of which 1,3-positions are bridged with an ansa chain.¹ The arene ring can rapidly flip in many cases, but when the flipping is restricted, metacyclophanes can exhibit stable planar chirality. Such an intriguing chiral metacyclophane unit can be observed in variable natural products like galeon and vancomycin.² Chiral metacyclophanes also constitute a key structural element of some pharmaceuticals³ and supramolecular host materials that capture small molecules⁴. Consequently, the development of methods to access chiral metacyclophane skeletons stereoselectively has attracted much attention.⁵⁻⁷

The author herein discloses a sequential process to expand orthocyclophanes **1** into their more strained constitutional isomers, metacyclophanes **2** (Scheme 1). In this transformation, 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** with planar chirality.

Scheme 1. Ring expansion reactions

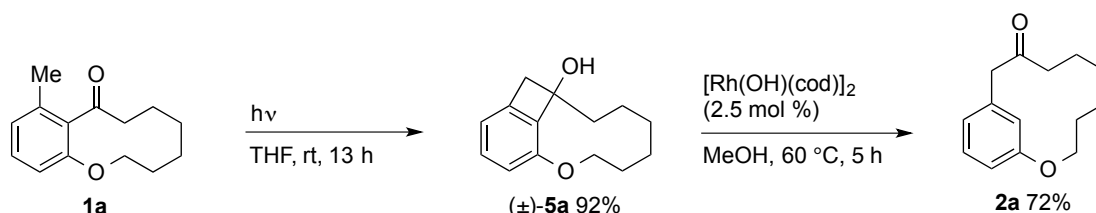


Results and Discussions

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 (Scheme 2). Photocyclization⁸ took place to afford benzocyclobutenol (±)-**5a** in 92% isolated yield. Subsequently, the benzocyclobutenol (±)-**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) bond⁹ 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 ($\delta = 3.67$ (s, 2H)), suggesting that the benzene ring rotates up and down freely across the ansa chain.

Scheme 2. Ring expansion **1a** to **2a**

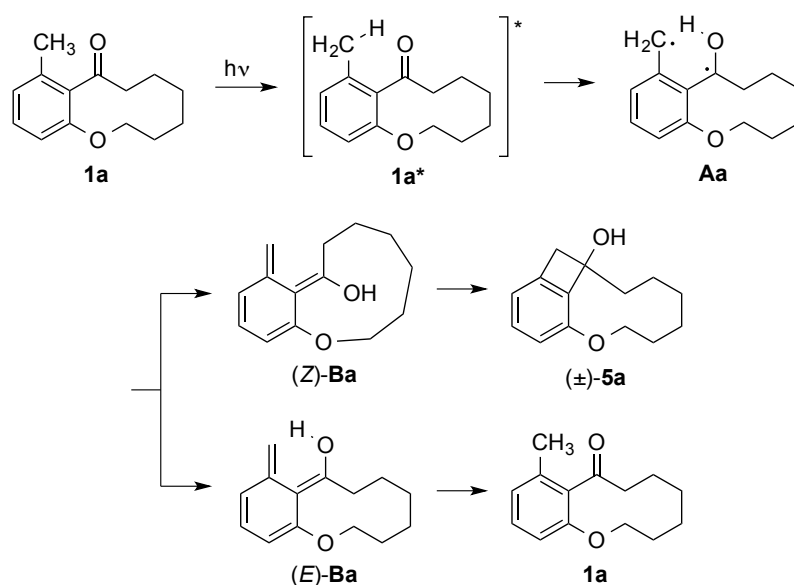


A two-step mechanistic scenario is depicted in Scheme 3. The first step is a photo-induced ring closing reaction (Scheme 3a). According to the mechanism originally proposed by Wagner *et al.*,^{8c} the ketone **1a** is electronically excited and the excited carbonyl group behaves as an oxyl radical to site-specifically abstract the benzylic hydrogen¹⁰. The resulting 1,4-biradical species **Aa**, possessing an *o*-phenylene linker, spontaneously furnishes an isomeric mixture of the *o*-quinodimethanes (*E*)- and (*Z*)-**Ba**.¹¹ The (*Z*)-isomer having an outward-oriented hydroxy group undergoes a 4 π -electrocyclic ring closure reaction to form benzocyclobutenol **(±)-5a**. On the other hand, the (*E*)-isomer having an inward-oriented hydroxy group undergoes facile 1,5-hydrogen shift to regenerate **1a** rather than the ring closure.

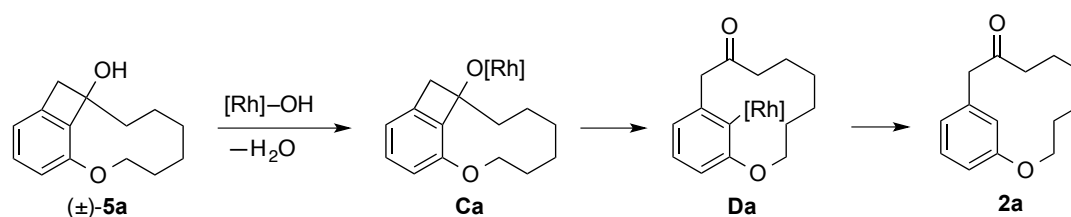
The second step is a ring-opening reaction promoted by the rhodium hydroxide complex (Scheme 3b). The hydroxyl group of **(±)-5a** is replaced with the rhodium hydroxide to generate rhodium benzocyclobutenolate **Ca**, in which the benzene ring likely π -coordinates to rhodium.¹² Next is followed by β -carbon elimination, for which the π -coordination facilitates site-selective cleavage of the C(sp²)–C(sp³) bond to furnish arylrhodium **Da**. Finally, protonation yields [9]metacyclophane **2a**. In order to evaluate 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) (Experimental section Fig. 1). The results suggest that **(±)-5a** and **2a** are thermodynamically less stable than **1a** by ca. 32.3 and 3.8 kcal/mol, respectively. The irreversible formation of highly energetic intermediate **(±)-5a** by the first photocyclization process enables to proceed the energetically uphill transformation from the reactant **1a** to its more strained constitutional isomer **2a**.

Scheme 3. Plausible mechanisms for the formation of **2a**

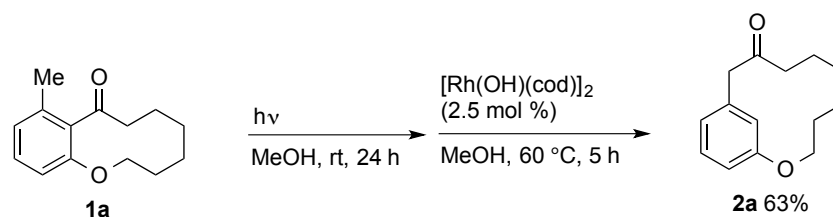
(a) 1st step



(b) 2nd step

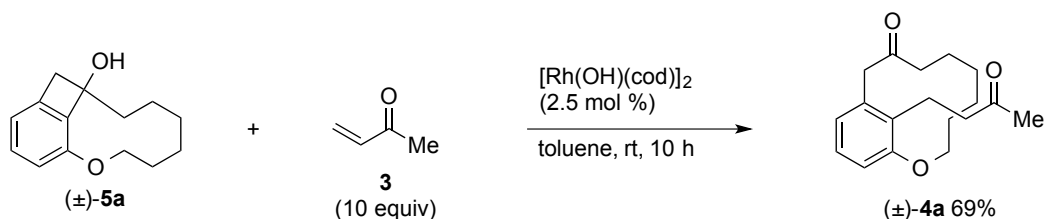


The author also succeeded in the transformation of orthocyclophane **1a** to metacyclophane **2a** in one flask. The methanol solution of orthocyclophane **1a** was irradiated with UV light at room temperature for 24 h, followed by the addition of a rhodium catalyst directly to the reaction mixture without the isolation of benzocyclobutenol **(±)-5a**. Metacyclophane **2a** was obtained in 63% isolated yield (Scheme 4).

Scheme 4. Synthesis of metacyclophane in one flask

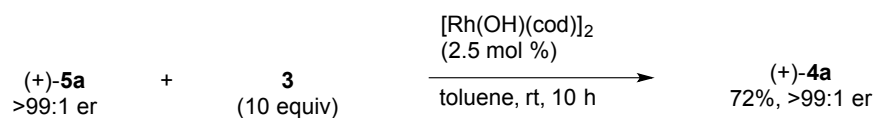
Next tried was utilizing the arylrhodium intermediate **D** for the subsequent C–C bond formation, aiming at the synthesis of planar chiral metacyclophanes. The racemic benzocyclobutenol ($\pm$)-**5a** was treated with a rhodium catalyst in the presence of methyl vinyl ketone **3** (10 equiv) in toluene at room temperature for 10 h (Scheme 5). 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 $\delta = 3.44$ (d, $J = 14.6$ Hz, 1 H) and $\delta = 3.95$ (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. The author assumes that the substituent derived from methyl vinyl ketone prohibits the flipping of the benzene ring to construct stable planar chirality.

Scheme 5. Planar chiral derivatives



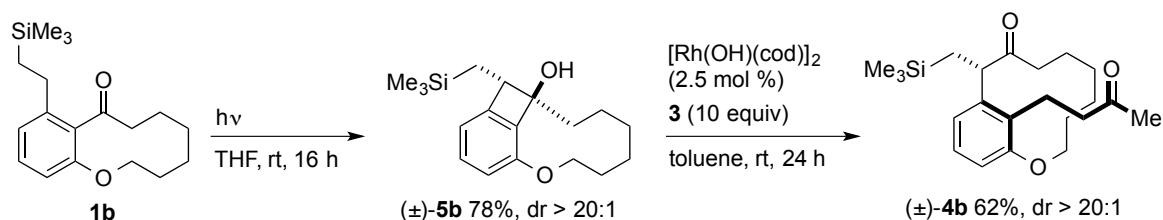
The interest was directed to the transition of stereochemistry through the ring opening/addition process, during which central chirality of benzocyclobutenol **5a** disappeared and planar chirality of **4a** was generated. The racemic mixture of benzocyclobutenol ($\pm$)-**5a** was successfully separated 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 $[\text{Rh}(\text{OH})(\text{cod})]_2$ catalyst afforded (+)-**4a** in 72% yield (Scheme 6). A chiral HPLC analysis showed that the enantiomeric purity was retained (>99:1 er). This result indicated the stereochemical integrity during the transfer of central chirality of **5a** to planar chirality of **4a**,¹³ letting the author examine the stereospecificity of chiral transfer in more detail.

Scheme 6. Enantiopure starting material

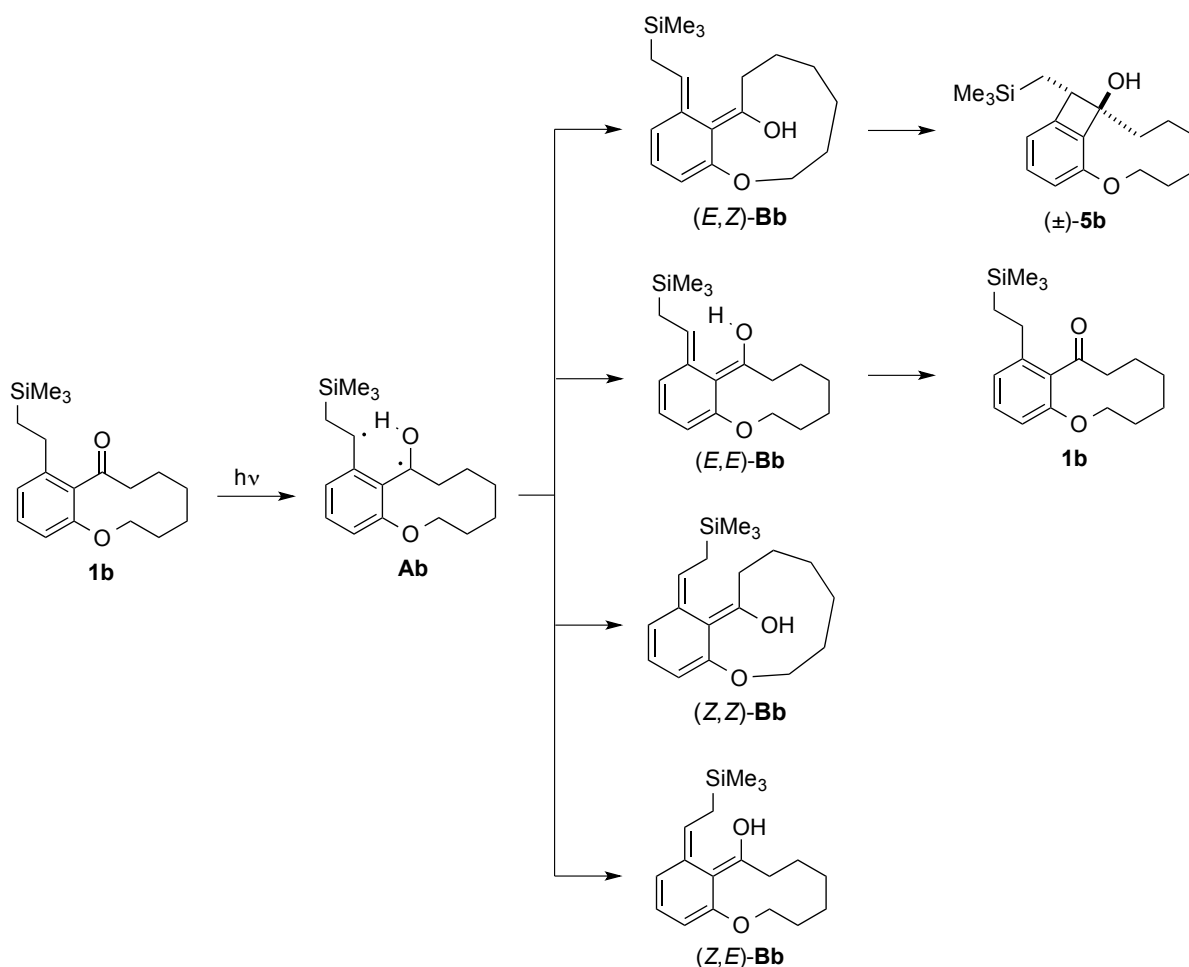


The ring expansion of orthocyclophane **1b** to metacyclophane ($\pm$)-**4b** was carried out (Scheme 7). The first photocyclization of **1b** afforded benzocyclobutenol ($\pm$)-**5b** in 78% isolated yield as a single diastereomer. It was determined by NOE analysis that the hydroxy group was trans to the (trimethylsilyl)methyl substituent. Subsequent treatment of ($\pm$)-**5b** with the rhodium catalyst in the presence of **3** (10 equiv) in toluene at room temperature for 24 h furnished [9]metacyclophane ($\pm$)-**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).

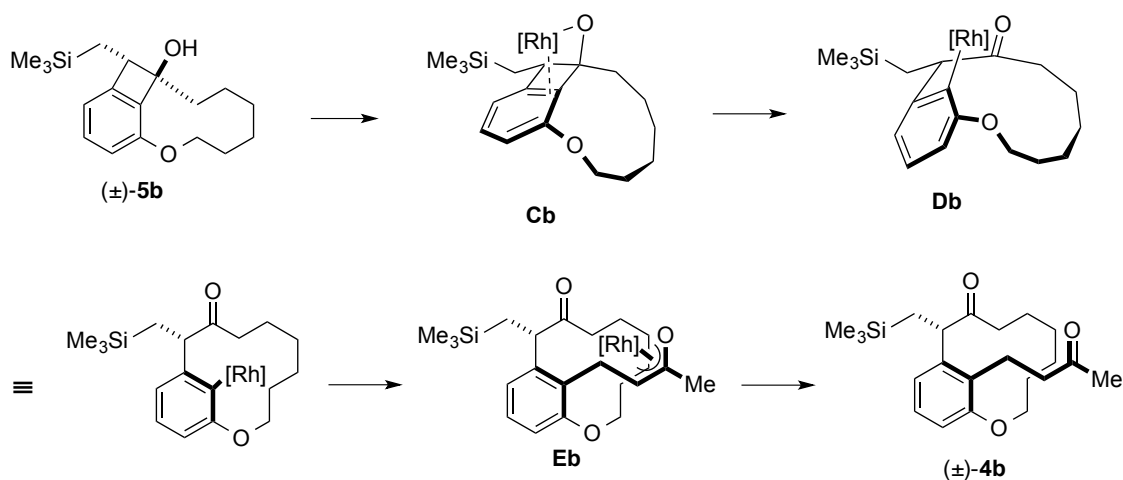
Scheme 7. Synthesis of cyclophane ($\pm$)-**4b** from **1b**



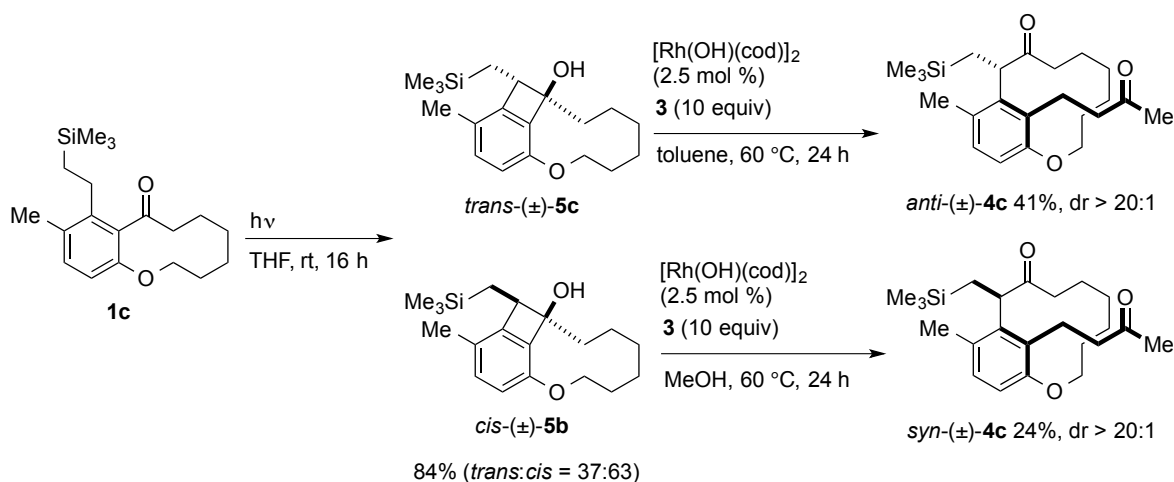
The explanation for the diastereoselectivity observed in the photocyclization step is shown in Scheme 8.^{8c} Although the 1,4-biradical species **Ab** generated from **1b** potentially gives rise to four stereoisomers (*E,Z*)-**Bb**, (*E,E*)-**Bb**, (*Z,Z*)-**Bb** and (*Z,E*)-**Bb**, the formation of (*Z,Z*)-**Bb** and (*Z,E*)-**Bb** is disfavored because of steric repulsion arising between the trimethylsilylmethyl group and the ansa chain. As with the cases of (*Z*)- and (*E*)-**Ba** in scheme 3a, 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 reverts to the starting ketone **1b** via facile 1,5-hydrogen shift.

Scheme 8. Reaction pathway from **1b** to (±)-**5b**

The second ring-opening step occurs with central-to-planar chirality transfer¹³ (Scheme 9). 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 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 (±)-**4b** stereoselectively.

Scheme 9. Reaction pathway from (±)-**5b** to **4b**

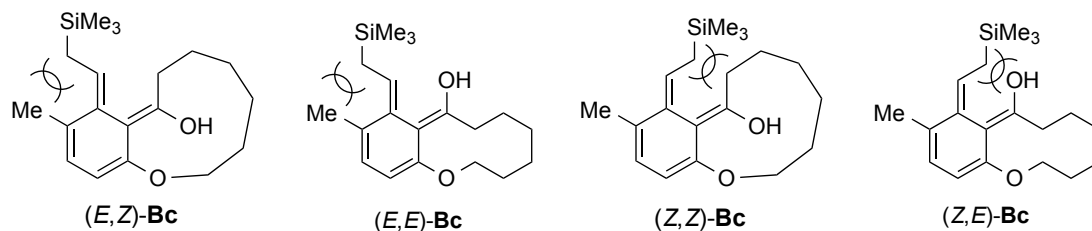
Stereoselective production of (±)-**4b** from (±)-**5b** provides a strong support for the validity of the stereospecificity of β -carbon elimination. Nonetheless, there remains a possibility that the formation of the diastereomer (±)-**4b** is favored over that of the other diastereomer simply due to thermodynamic or kinetic reasons, rather than a mechanistic consequence. In order to examine this possibility, the author next carried out the rhodium-catalyzed reactions of diastereomeric benzocyclobutenols, *trans*- and *cis*-(±)-**5c**, which were prepared from **1c** having an additional methyl group next to the trimethylsilyl ethyl substituent (Scheme 10).

Scheme 10. Synthesis of metacyclophane (±)-**4c** from **1c**

The result of the first photocyclization step of **1c** contrasted with that of **1b**, affording a diastereomer mixture of *trans*-(±)-**5c** and *cis*-(±)-**5c** (84%, 37:63). While there are four stereoisomers possibly generated from the biradical intermediate (Scheme 11), 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 (*Z,Z*)-**Bc** is more favored than (*E,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*-(±)-**5c** and *cis*-(±)-**5c**, respectively.

Scheme 11. Structures of possible quinodimethane intermediates **B**



Then, the two diastereomers *trans*-(±)-**5c** and *cis*-(±)-**5c** were separated by chromatography on silica gel, and each isolated diastereomer was subjected to the second ring-opening reaction. The diastereomer *trans*-(±)-**5c** with its hydroxy group directing upward (that is, *trans* to the (trimethylsilyl)methyl substituent) selectively furnished *anti*-(±)-**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*-(±)-**5c** with its hydroxy group directing downward (that is, *cis* to the (trimethylsilyl)methyl substituent) selectively furnished *syn*-(±)-**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*-(±)-**5c** and *cis*-(±)-**5c** to establish that β-aryl elimination occurs in a stereospecific fashion.

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

Table 1. Ring expansion of **1**

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

Conclusions

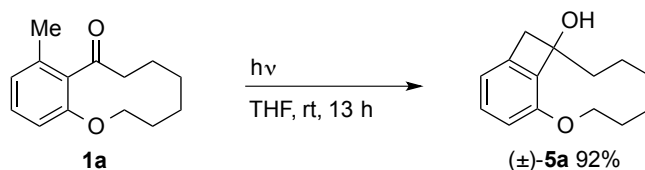
The author has described a ring-expanding pathway from orthocyclophanes **1** to their constitutional isomers, metacyclophanes **2** by means of the sequential action of light and rhodium. Formally, the non-strained C–H and C–C bonds are cleaved and exchanged to form a product that is energetically uphill. 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-catalyzed C–C bond cleavage.

Experimental section

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 x 250 mm column.

Materials. Anhydrous THF, DCM, and Et_2O were purchased from Kanto Chemical Co. Anhydrous MeOH and DMF were purchased from Wako Pure Chemical Industries. Toluene and 1,4-dioxane were distilled from sodium/benzophenone ketyl. Methyl vinyl ketone was distilled from K_2CO_3 and CaCl_2 prior to use. **B1**,¹⁴ **C1**,¹⁴ **G1**,¹⁵ **H1**,¹⁶ $[\text{Rh}(\text{OH})(\text{cod})]_2$,¹⁷ and $\text{Ru}(\text{H})_2(\text{CO})(\text{PPh}_3)_3$ ¹⁸ were prepared according to the literature procedures. All other commercially available chemical resources were used as received without further purification.

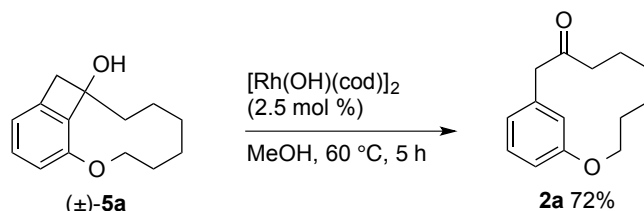
Photocyclization of orthocyclophane **1a**



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/ethyl acetate = 5/1) to afford (±)-**5a** (20.0 mg, 0.092 mmol, 92%); IR (neat): 3385, 2920, 1603, 1456, 1273, 1047, 775 cm^{-1} ; ^1H NMR: $\delta = 1.12$ – 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

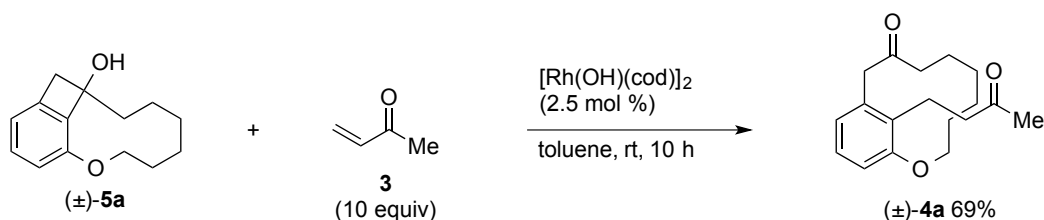
(ddd, $J = 10.4, 6.4, 2.0$ Hz, 1H), 6.71 (dd, $J = 8.4, 0.4$ Hz, 1H), 6.77 (dd, $J = 7.2, 0.8$ Hz, 1H), 7.23 (dd, $J = 8.0, 7.2$ Hz, 1H); ^{13}C NMR: $\delta = 21.4, 24.6, 27.5, 28.9, 38.3, 48.4, 72.6, 80.4, 115.0, 117.0, 130.9, 137.2, 142.5, 154.3$; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 219.1380. Found m/z 219.1376.

Rhodium-catalyzed ring opening of ($\pm$)-**5a**



A mixture containing $[\text{Rh}(\text{OH})(\text{cod})]_2$ (1.1 mg, 2.5 mmol, 2.5 mol %) and 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[®], eluted with ethyl acetate and evaporated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford metacyclophane **2a** (15.7 mg, 0.072 mmol, 72%); IR (neat): 2922, 1697, 1587, 1161, 783 cm^{-1} ; ^1H NMR: $\delta = 0.98\text{--}1.11$ (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: $\delta = 22.4, 22.7, 24.4, 31.3, 35.8, 50.9, 63.4, 112.1, 116.3, 121.7, 130.4, 135.9, 159.9, 209.8$; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 219.1380. Found m/z 219.1377.

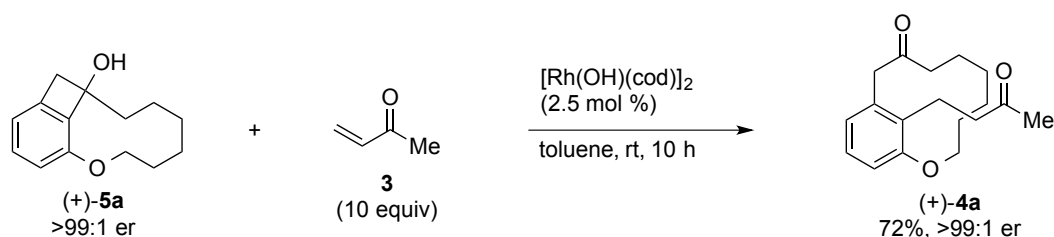
Synthesis of metacyclophane ($\pm$)-**4a**



A mixture containing $[\text{Rh}(\text{OH})(\text{cod})]_2$ (1.2 mg, 2.5 mmol, 2.5 mol %), methyl vinyl ketone **3** (81.6 ml, 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/ethyl acetate = 5/1) to afford ($\pm$)-**4a** (19.9 mg, 0.069 mmol, 69%); IR (neat):

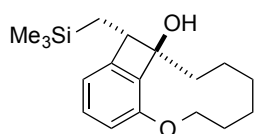
2941, 1705, 1454, 1232, 910, 729 cm^{-1} ; ^1H NMR: δ = 0.25–0.45 (m, 1H), 0.51–0.68 (m, 1H), 0.77–0.98 (m, 3H), 1.27–1.61 (m, 3H), 1.93–2.13 (m, 5H), 2.50 (ddd, J = 17.6, 9.2, 6.4 Hz, 1H), 2.61 (ddd, J = 17.6, 9.2, 5.6 Hz, 1H), 2.88 (ddd, J = 13.6, 8.8, 6.4 Hz, 1H), 3.30 (ddd, J = 14.4, 9.6, 5.6 Hz, 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, 209.3; HRMS (APCI): Calcd for $\text{C}_{18}\text{H}_{25}\text{O}_3$, $[\text{M}+\text{H}]^+$ 289.1798. Found m/z 289.1792.

Synthesis of (+)-4a



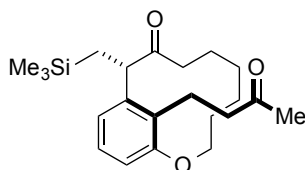
The racemic mixture of ($\pm$)-**5a** was separated by chiral preparative HPLC (Daicel CHIRALPAK OZ-H column, hexane:*i*-PrOH = 90:10). $[\alpha]_{\text{D}}^{25}$ = +74.0 (c = 1.1×10^{-2} M in CHCl_3). A mixture containing $[\text{Rh}(\text{OH})(\text{cod})]_2$ (1.7 mg, 3.8 mmol, 2.5 mol %), methyl vinyl 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/ethyl acetate = 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), $[\alpha]_{\text{D}}^{25}$ = +68.4 (c = 2.1×10^{-2} M in CHCl_3).

5b:

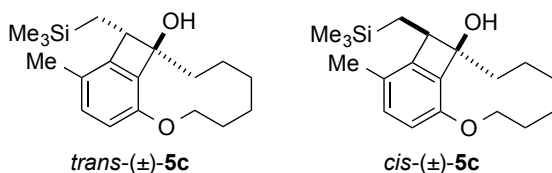


IR (neat): 3331, 2951, 1601, 1464, 1271, 1244, 1005, 854 cm^{-1} ; ^1H NMR: δ = 0.13 (s, 9H), 0.81 (dd, J = 14.4, 11.2 Hz, 1H), 1.03 (dd, J = 14.8, 4.0 Hz, 1H), 1.07–1.22 (m,

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: $\delta = -0.8, 16.8, 21.2, 25.4, 27.2, 29.1, 34.1, 55.7, 73.0, 82.7, 114.9, 116.5, 130.9, 136.4, 148.1, 154.4$; HRMS (APCI): Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_2\text{SiNa}$, $[\text{M}+\text{Na}]^+ 327.1751$. Found $m/z 327.1743$.

4b:

IR (neat): 2947, 1709, 1454, 1242, 980, 831 cm^{-1} ; ^1H NMR: $\delta = 0.03$ (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: $\delta = -1.0, 15.5, 20.3, 21.7, 23.0, 26.3, 26.4, 29.8, 37.9, 45.0, 51.6, 70.3, 119.1, 121.7, 126.9, 133.5, 138.4, 155.8, 207.8, 209.9$; HRMS (APCI): Calcd for $\text{C}_{22}\text{H}_{35}\text{O}_3\text{Si}$, $[\text{M}+\text{H}]^+ 375.2350$. Found $m/z 375.2340$.

5c:

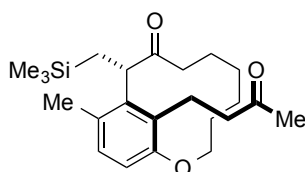
5c was obtained as a diastereomer mixture that was separated by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 10/1).

trans-**5c**. IR (neat): 3423, 2928, 1618, 1493, 1246, 1020, 837 cm^{-1} ; ^1H NMR: $\delta = 0.12$ (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: $\delta = -0.8, 15.8, 16.2, 21.5,$

25.6, 27.1, 29.0, 34.3, 54.9, 73.1, 82.2, 114.9, 126.2, 131.6, 135.7, 145.8, 152.3; HRMS (APCI): Calcd for $C_{19}H_{30}O_2SiNa$, $[M+Na]^+$ 341.1907. Found m/z 341.1899.

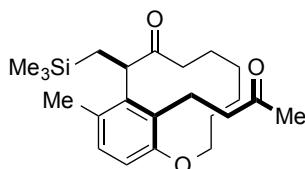
cis-**5c**. IR (neat): 3396, 2926, 1491, 1244, 835 cm^{-1} ; 1H NMR: δ = -0.09 (s, 9H), 0.88–1.05 (m, 2H), 1.10–1.29 (m, 1H), 1.33–1.60 (m, 5H), 1.62–1.78 (m, 1H), 1.82–2.02 (m, 2H), 2.09–2.29 (m, 5H), 3.33 (dd, J = 10.0, 4.4 Hz, 1H), 3.84 (ddd, J = 10.4, 8.8, 1.6 Hz, 1H), 4.53 (ddd, J = 10.8, 6.4, 2.0 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, 152.9; HRMS (APCI): Calcd for $C_{19}H_{30}O_2SiNa$, $[M+Na]^+$ 341.1907. Found m/z 341.1902.

***anti*-4c:**



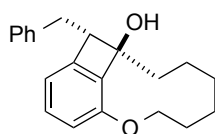
The reaction was performed at 60 °C. IR (neat): 2930, 1697, 1450, 1248, 837 cm^{-1} ; 1H NMR: δ = -0.02 (s, 9H), 0.74–1.07 (m, 5H), 1.20–1.45 (m, 4H), 1.77–1.90 (m, 2H), 2.12 (s, 3H), 2.19 (s, 3H), 2.25 (ddd, J = 12.0, 4.0, 4.0 Hz, 1H), 2.44 (ddd, J = 18.0, 11.2, 4.4 Hz, 1H), 2.76 (ddd, J = 18.0, 11.2, 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, 209.0; HRMS (APCI): Calcd for $C_{23}H_{37}O_3Si$, $[M+H]^+$ 389.2506. Found m/z 389.2498.

***syn*-4c:**

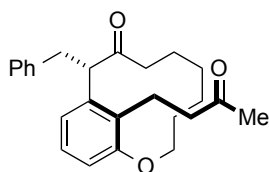


The reaction was performed at 60 °C in MeOH instead of toluene. IR (neat): 2949, 1711, 1454, 1246, 980, 833 cm^{-1} ; 1H NMR: δ = 0.02 (s, 9H), 0.71–0.86 (m, 2H), 0.90–1.16 (m, 2H), 1.16–1.32 (m, 2H), 1.48–1.85 (m, 5H), 2.01–2.14 (m, 4H), 2.34 (ddd, J = 16.4, 11.6, 4.8 Hz, 1H), 2.41 (s, 3H), 2.55 (ddd, 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, 209.6; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{37}\text{O}_3\text{Si}$, $[\text{M}+\text{H}]^+$ 389.2506. Found m/z 389.2499.

5d:

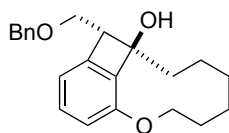
IR (neat): 3331, 2918, 1601, 1454, 1273, 1009, 702 cm^{-1} ; ^1H NMR: δ = 1.12–1.30 (m, 1H), 1.38–1.64 (m, 5H), 1.68–1.80 (m, 1H), 1.87–2.03 (m, 1H), 2.05–2.15 (m, 1H), 2.18–2.32 (m, 1H), 2.84 (dd, J = 14.0, 10.0 Hz, 1H), 3.13 (dd, J = 14.0, 6.0 Hz, 1H), 3.70 (dd, J = 10.4, 6.4 Hz, 1H), 3.87 (ddd, J = 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, 154.4; HRMS (APCI): Calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2$, $[\text{M}+\text{H}]^+$ 309.18549. Found m/z 309.1840.

4d:

MeOH was employed as a solvent instead of toluene. IR (neat): 2855, 1715, 1699, 1456, 1038, 978, 700 cm^{-1} ; ^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,

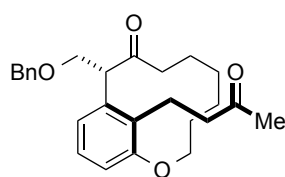
155.2, 207.9, 209.1; HRMS (APCI): Calcd for $C_{25}H_{31}O_3$, $[M+H]^+$ 379.2268. Found m/z 379.2256.

5e:

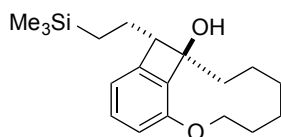


IR (neat): 3393, 2928, 1603, 1454, 1271, 1080, 1026, 743, 696 cm^{-1} ; 1H NMR: δ = 1.04–1.22 (m, 1H), 1.33–1.77 (m, 6H), 1.80–2.14 (m, 3H), 2.16–2.30 (m, 1H), 3.43 (dd, J = 9.2, 5.6 Hz, 1H), 3.68 (t, J = 6.8 Hz, 2H), 3.86 (ddd, J = 10.8, 1.6, 1.6 Hz, 1H), 4.51–4.62 (m, 3H), 6.71 (d, J = 6.4 Hz, 1H), 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 = 21.3, 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, 154.4; HRMS (APCI): Calcd for $C_{23}H_{29}O_3$, $[M+H]^+$ 353.2111. Found m/z 353.2100.

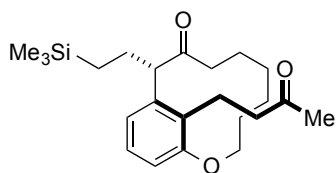
4e:



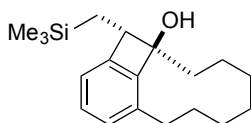
MeOH was employed as a solvent instead of toluene. IR (neat): 2943, 1705, 1454, 1240, 1099, 733 cm^{-1} ; 1H NMR: δ = -0.29–0.13 (m, 1H), 0.69–0.82 (m, 1H), 0.91–1.10 (m, 3H), 1.15–1.45 (m, 3H), 1.80–1.92 (m, 4H), 2.13–2.24 (m, 1H), 2.30–2.40 (m, 1H), 2.42–2.67 (m, 3H), 3.21 (ddd, J = 13.6, 10.0, 5.6 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); ^{13}C 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, 209.5; HRMS (APCI): Calcd for $C_{27}H_{35}O_4$, $[M+H]^+$ 423.2530. Found m/z 423.2519.

5f:

IR (neat): 3385, 2926, 1603, 1456, 1244, 833 cm^{-1} ; ^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); ^{13}C 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, 154.4; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{30}\text{O}_2\text{SiNa}$, $[\text{M}+\text{Na}]^+$ 341.1907. Found m/z 341.1899.

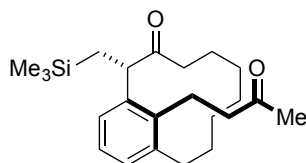
4f:

IR (neat): 2939, 1713, 1692, 1452, 1248, 837 cm^{-1} ; ^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); ^{13}C 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, 210.3; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{37}\text{O}_3\text{Si}$, $[\text{M}+\text{H}]^+$ 389.2506. Found m/z 389.2495.

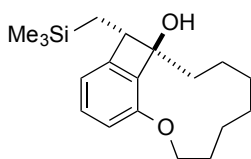
5g:

IR (neat): 3319, 2926, 1246, 849 cm^{-1} ; ^1H NMR: δ = 0.13 (s, 9H), 0.75–1.02 (m, 3H),

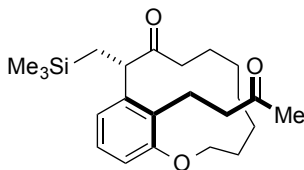
1.07–1.46 (m, 6H), 1.48–1.79 (m, 4H), 1.94 (ddd, $J = 14.8, 6.0, 2.8$ Hz, 1H), 2.08 (ddd, $J = 15.2, 10.8, 5.6$ Hz, 1H), 2.65 (ddd, $J = 14.0, 4.0, 4.0$ Hz, 1H), 2.79 (ddd, $J = 13.2, 13.2, 4.0$ Hz, 1H), 3.29 (dd, $J = 12.0, 3.2$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 7.23 (dd, $J = 7.6, 7.6$ Hz, 1H); ^{13}C NMR: $\delta = -0.8, 16.9, 20.2, 20.5, 20.9, 27.2, 27.5, 28.5, 31.5, 55.1, 85.9, 119.9, 127.3, 129.6, 137.3, 146.8, 147.1$; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{31}\text{O}_2\text{Si}$, $[\text{M}+\text{H}]^+$ 303.2139. Found m/z 303.2130.

4g:

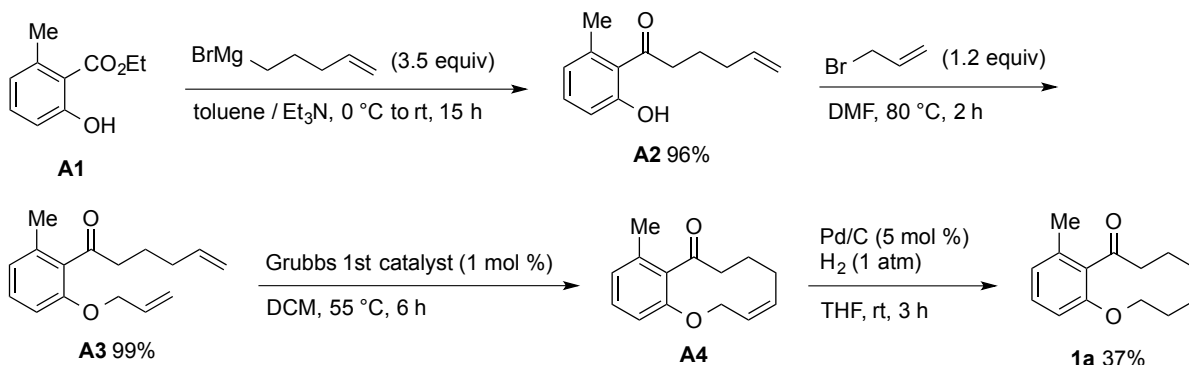
The reaction was performed at 60 °C. IR (neat): 2945, 1715, 1697, 1248, 837 cm^{-1} ; ^1H NMR: $\delta = -0.48$ – 0.36 (m, 1H), 0.052 (s, 9H), 0.46– 0.57 (m, 1H), 0.69– 0.84 (m, 3H), 1.13– 1.30 (m, 4H), 1.48– 1.56 (m, 1H), 1.67– 1.85 (m, 3H), 2.09 (s, 3H), 2.21 (ddd, $J = 10.0, 7.6, 2.8$ Hz, 1H), 2.38– 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); ^{13}C NMR: $\delta = -0.8, 16.6, 22.9, 23.4, 24.7, 25.06, 25.12, 26.5, 29.8, 32.8, 34.0, 45.4, 53.4, 125.4, 127.0, 130.1, 136.8, 139.8, 141.4, 207.5, 211.5$; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{37}\text{O}_2\text{Si}$, $[\text{M}+\text{H}]^+$ 373.2557. Found m/z 373.2548.

5h:

IR (neat): 3385, 2868, 1593, 1474, 1244, 1038, 833 cm^{-1} ; ^1H NMR: $\delta = 0.13$ (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); ^{13}C NMR: $\delta = -0.7, 16.7, 23.4, 23.6, 26.8, 27.2, 28.0, 33.8, 55.7, 69.1, 82.7, 112.1, 115.9, 130.6, 135.5, 148.7, 153.0$; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{30}\text{O}_2\text{SiNa}$, $[\text{M}+\text{Na}]^+$ 341.1907. Found m/z 341.1899.

4h:

IR (neat): 2932, 1711, 1246, 835 cm^{-1} ; ^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); ^{13}C 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, 210.8; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{37}\text{O}_3\text{Si}$, $[\text{M}+\text{H}]^+$ 389.2506. Found m/z 389.2494.

Synthesis of 1a

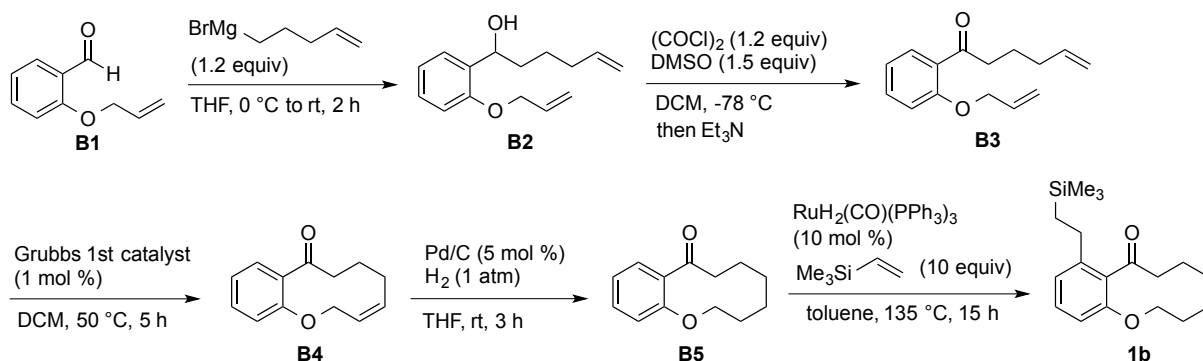
A solution of 4-pentenylmagnesium bromide in Et_2O (1.0 M, 35.0 mL, 35.0 mmol) and triethylamine (5.0 mL, 37.0 mmol) in anhydrous toluene (20 mL) was cooled to 0 °C. 6-Methylsalicylate **A1** (1.80 g, 10.0 mmol) in anhydrous toluene (4 mL) was added dropwise and the reaction mixture was stirred at room temperature for 12 h. A saturated solution of ammonium chloride (10 mL) was added and the mixture was extracted with ethyl acetate, washed with water and brine, dried over MgSO_4 , and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to afford ketone **A2** (1.96 g, 9.6 mmol, 96%); IR (neat): 3337, 2934, 1680, 1464, 1285, 912, 779 cm^{-1} ; ^1H NMR: δ = 1.85 (tt, J = 7.2, 7.2 Hz, 2H), 2.09–2.18 (m, 2H), 2.56 (s, 3H), 2.94 (t, J = 7.6 Hz, 2H), 4.95–5.07 (m, 2H), 5.80 (ddt,

$J = 16.8, 10.4, 6.4$ Hz, 1H), 6.68–6.74 (m, 1H), 6.82 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.25 (dd, $J = 8.0, 7.6$ Hz, 1H), 11.62 (s, 1H); ^{13}C NMR: $\delta = 23.8, 24.1, 33.1, 43.6, 115.4, 116.2, 122.5, 123.1, 134.0, 137.8, 138.6, 161.5, 208.8$; HRMS (APCI): Calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2$, $[\text{M}+\text{H}]^+ 205.1223$. Found m/z 205.1219.

To a stirred solution of **A2** (1.96 g, 9.6 mmol) in DMF (30 mL) were added K_2CO_3 (1.94 g, 14.0 mmol) and allyl bromide (1.80 g, 15.0 mmol). After stirring the reaction mixture for 2 h at 80 °C, water was added and extracted with ethyl acetate, washed with water and brine, dried over MgSO_4 , and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford **A3** (2.35 g, 9.5 mmol, 99%); IR (neat): 2928, 1695, 1466, 1259, 991, 912, 775 cm^{-1} ; ^1H NMR: $\delta = 1.80$ (tt, $J = 7.2, 7.2$ Hz, 2H), 2.07–2.17 (m, 2H), 2.21 (s, 3H), 2.80 (t, $J = 7.6$ Hz, 2H), 4.53 (ddd, $J = 5.2, 1.2, 1.2$ Hz, 2H), 4.98 (ddt, $J = 10.4, 2.4, 1.2$ Hz, 1H), 5.02 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H), 5.25 (ddt, $J = 10.4, 1.2, 1.2$ Hz, 1H), 5.35 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H), 5.80 (ddt, $J = 16.8, 10.0, 6.4$ Hz, 1H), 5.99 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 1H), 6.79 (d, $J = 7.6$ Hz, 1H), 7.18 (dd, $J = 8.0, 8.0$ Hz, 1H); ^{13}C NMR: $\delta = 18.9, 22.7, 33.1, 43.8, 69.1, 109.5, 115.0, 117.5, 123.0, 129.5, 131.6, 132.8, 135.4, 138.2, 155.0, 207.9$; HRMS (APCI): Calcd for $\text{C}_{16}\text{H}_{21}\text{O}_2$, $[\text{M}+\text{H}]^+ 245.1536$. Found m/z 245.1531.

To a solution of Grubbs 1st generation catalyst (24.6 mg, 0.030 mmol) in anhydrous CH_2Cl_2 (200 mL) were added **A3** (733 mg, 3.0 mmol) at 55 °C. After stirring for 6 h, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate) to afford crude **A4**, which was subjected to the next hydrogenation reaction without further purification.

A mixture of **A4** and Pd/C (10 wt. %, 150 mg) in anhydrous THF (15 mL) was stirred under hydrogen atmosphere (1 atm) at room temperature for 3 h. The reaction mixture was filtered through a celite pad and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford **1a** (242 mg, 1.11 mmol, 37%); IR (neat): 2928, 1693, 1460, 1259, 1072, 777 cm^{-1} ; ^1H NMR: $\delta = 1.51$ – 1.69 (m, 4H), 1.72–1.82 (m, 4H), 2.23 (s, 3H), 2.57–2.63 (m, 2H), 4.15 (t, $J = 5.2$ Hz, 2H), 6.77 (d, $J = 8.4$ Hz, 1H), 6.81 (d, $J = 7.6$ Hz, 1H), 7.20 (dd, $J = 8.0, 8.0$ Hz, 1H); ^{13}C NMR: $\delta = 18.7, 24.0, 25.4, 26.6, 27.6, 43.1, 71.4, 111.0, 123.4, 129.7, 132.5, 135.1, 156.4, 209.4$; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+ 219.1380$. Found m/z 219.1375.

Synthesis of **1b**

To a stirred solution of 2-(allyloxy)benzaldehyde **B1** (1.62 g, 10.0 mmol) in anhydrous THF (30 mL) at 0 °C was added 4-pentenylmagnesium bromide in anhydrous Et_2O (1.0 M, 12.0 mL, 12.0 mmol) slowly. After stirring for 2 h at room temperature, saturated NH_4Cl aq was added at 0 °C. The mixture was extracted with Et_2O , washed with water and brine, dried over Na_2SO_4 , and evaporated to afford crude **B2**. This compound was used without further purification.

To a solution of oxalyl chloride (1.0 mL, 11.7 mmol) in anhydrous CH_2Cl_2 was added dropwise DMSO (1.1 mL, 15.5 mmol) at -78 °C. After stirring for 20 min., a solution of crude **B2** in anhydrous CH_2Cl_2 (10 mL) was added slowly to the mixture. The reaction mixture was stirred for 1 h at -78 °C, Et_3N (7.5 mL) was added by syringe. After stirring at room temperature for 40 min., water was added. The mixture was extracted with CH_2Cl_2 , washed with water and brine, dried over MgSO_4 , and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford **B3** (1.64 g, 7.13 mmol, 71%); IR (neat): 2934, 1670, 1595, 1448, 1234, 991, 752 cm^{-1} ; ^1H NMR: δ = 1.79 (tt, J = 7.2, 7.2 Hz, 2H), 2.07–2.15 (m, 2H), 3.01 (t, J = 7.2 Hz, 2H), 4.62 (dt, J = 5.2, 1.6 Hz, 2H), 4.93–4.98 (m, 1H), 5.02 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H), 5.29–5.35 (m, 1H), 5.42 (ddt, J = 17.2, 1.6, 1.2 Hz, 1H), 5.80 (ddt, J = 16.8, 10.4, 6.4 Hz, 1H), 6.01–6.13 (m, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.97–7.03 (m, 1H), 7.38–7.45 (m, 1H), 7.65 (dd, J = 8.0, 2.0 Hz, 1H); ^{13}C NMR: δ = 23.5, 33.3, 43.1, 69.3, 112.6, 114.9, 118.1, 120.8, 128.9, 130.1, 132.6, 133.0, 138.3, 157.3, 202.8; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 231.1380. Found m/z 231.1377.

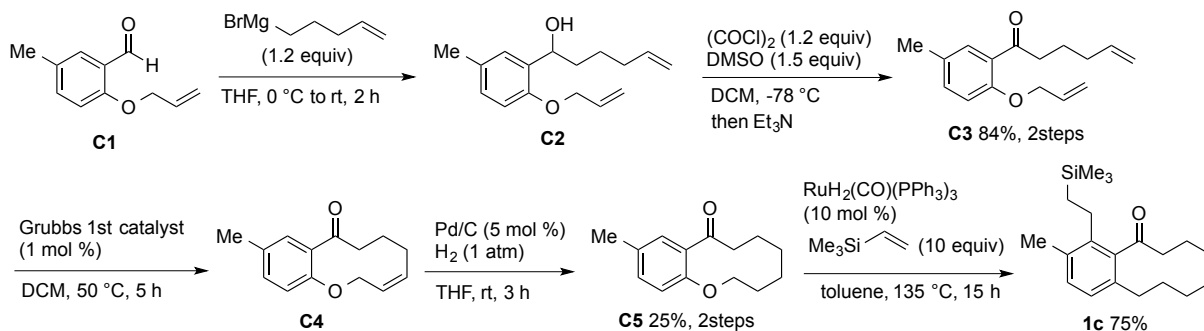
To a solution of Grubbs 1st generation catalyst in anhydrous CH_2Cl_2 (100 mL) was added **B3** (230 mg, 1.0 mmol) at 50 °C. After stirring for 5 h, the reaction mixture was concentrated. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford crude **B4**, which was subjected to the next hydrogenation

reaction without further purification.

A mixture of **B4** and Pd/C (10 wt. %, 53.0 mg) in anhydrous THF (10 mL) was stirred under hydrogen atmosphere (1 atm) at room temperature for 3 h. The reaction mixture was filtered through a celite pad and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford **B5** (75 mg, 0.37 mmol, 37%); IR (neat): 2926, 1668, 1595, 1450, 1292, 1003, 752 cm^{-1} ; ^1H NMR: δ = 1.53–1.64 (m, 2H), 1.69–1.90 (m, 6H), 2.78 (t, J = 7.2 Hz, 2H), 4.15 (t, J = 6.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.98–7.04 (m, 1H), 7.41–7.47 (m, 1H), 7.67 (dd, J = 7.6, 1.6 Hz, 1H); ^{13}C NMR: δ = 23.0, 23.6, 27.4, 27.5, 41.3, 70.1, 114.0, 121.1, 129.71, 129.74, 133.2, 158.3, 203.9; HRMS (APCI): Calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2$, $[\text{M}+\text{H}]^+$ 205.1223. Found m/z 205.1218.

A mixture containing $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (9.2 mg, 1.0 mmol, 10 mol %), vinyltrimethylsilane (100 mg, 1.0 mmol), and **B5** (20.4 mg, 0.10 mmol) in toluene (0.10 mL) was stirred at 135 °C for 15 h. After being cooled to room temperature, 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/ethyl acetate = 10/1) to afford **1b** (25.5 mg, 0.084 mmol, 84%); IR (neat): 2930, 1695, 1456, 1246, 831 cm^{-1} ; ^1H NMR: δ = 0.00 (s, 9H), 0.74–0.85 (m, 2H), 1.51–1.69 (m, 4H), 1.72–1.84 (m, 4H), 2.44–2.53 (m, 2H), 2.58–2.65 (m, 2H), 4.14 (t, J = 5.2 Hz, 2H), 6.75 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 7.23 (dd, J = 8.0, 8.0 Hz, 1H); ^{13}C NMR: δ = -1.9, 19.4, 24.1, 25.3, 26.5, 26.9, 27.7, 43.3, 71.5, 110.7, 121.7, 129.9, 131.8, 143.0, 156.4, 209.2; HRMS (APCI): Calcd for $\text{C}_{18}\text{H}_{29}\text{O}_2\text{Si}$, $[\text{M}+\text{H}]^+$ 305.1931. Found m/z 305.1923.

Synthesis of 1c



1c was synthesized from **C3** in the same way as **1b** from **B1**.

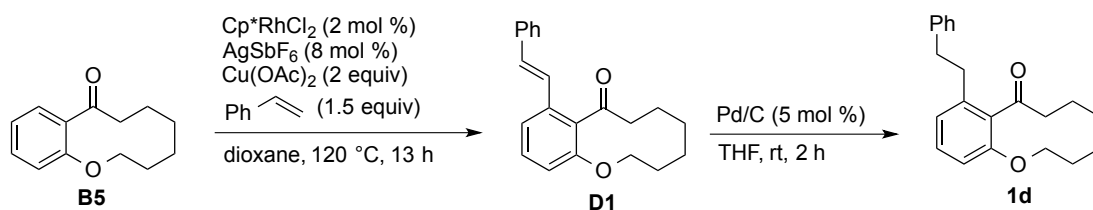
C3: IR (neat): 2926, 1670, 1495, 1236, 991, 910, 806 cm^{-1} ; ^1H NMR: δ = 1.78 (tt, J =

7.6, 7.2 Hz, 2H), 2.07–2.15 (m, 2H), 2.29 (s, 3H), 3.00 (t, $J = 7.6$ Hz, 2H), 4.59 (ddd, $J = 5.2, 1.6, 1.6$ Hz, 2H), 4.96 (ddt, $J = 10.4, 2.0, 1.2$ Hz, 1H), 5.02 (ddt, $J = 17.2, 2.0, 1.6$ Hz, 1H), 5.30 (ddt, $J = 10.4, 1.6, 1.2$ Hz, 1H), 5.41 (ddt, $J = 17.2, 1.6, 1.6$ Hz, 1H), 5.80 (ddt, $J = 16.8, 10.0, 6.8$ Hz, 1H), 6.06 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 7.21 (dd, $J = 8.4, 0.4$ Hz, 1H), 7.45 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR: $\delta = 20.2, 23.6, 33.3, 43.2, 69.4, 112.7, 114.8, 117.9, 128.6, 130.1, 130.4, 132.8, 133.5, 138.3, 155.3, 203.1$; HRMS (APCI): Calcd for $\text{C}_{16}\text{H}_{21}\text{O}_2$, $[\text{M}+\text{H}]^+$ 245.1536. Found m/z 245.1533.

C5: IR (neat): 2924, 1668, 1607, 1495, 1283, 1248, 812 cm^{-1} ; ^1H NMR: $\delta = 1.50$ – 1.60 (m, 2H), 1.66– 1.89 (m, 6H), 2.27 (s, 3H), 2.75 (t, $J = 6.8$ Hz, 2H), 4.08 (t, $J = 6.4$ Hz, 2H), 6.83 (d, $J = 8.0$ Hz, 1H), 7.17– 7.23 (m, 1H), 7.43 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR: $\delta = 20.3, 23.1, 23.5, 27.1, 27.4, 41.2, 70.3, 114.3, 129.3, 129.7, 130.5, 133.7, 156.2, 204.0$; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 219.1380. Found m/z 219.1375.

1c: IR (neat): 2932, 1695, 1464, 1246, 833 cm^{-1} ; ^1H NMR: $\delta = 0.03$ (s, 9H), 0.66– 0.77 (m, 2H), 1.49– 1.70 (m, 4H), 1.70– 1.83 (m, 4H), 2.23 (s, 3H), 2.37– 2.45 (m, 2H), 2.57– 2.65 (m, 2H), 4.11 (t, $J = 5.2$ Hz, 2H), 6.67 (d, $J = 8.4$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CD_3CN): $\delta = -2.0, 18.5, 18.9, 24.88, 24.93, 26.3, 27.4, 28.6, 44.6, 72.7, 112.1, 129.8, 132.5, 133.2, 141.2, 155.5, 210.2$; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{31}\text{O}_2\text{Si}$, $[\text{M}+\text{H}]^+$ 319.2088. Found m/z 319.2079.

Synthesis of 1d

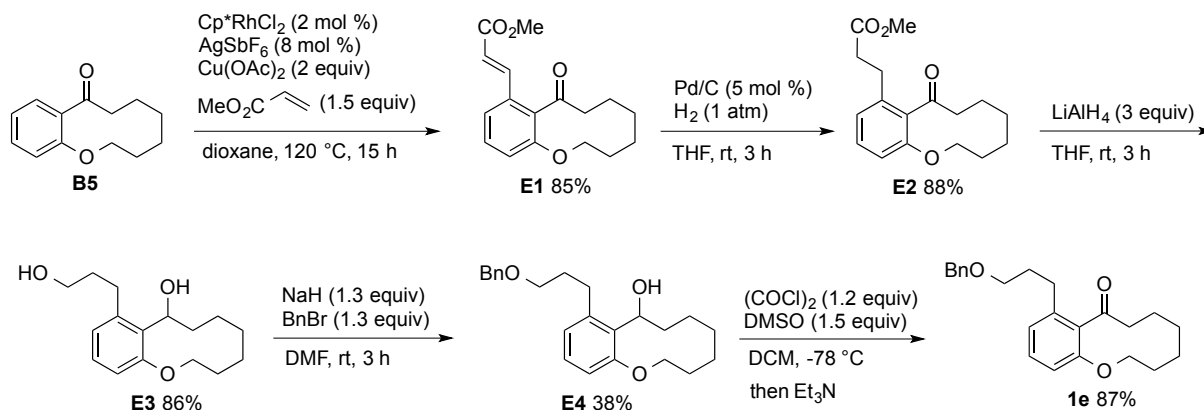


A mixture containing Cp^*RhCl_2 (3.7 mg, 6.0 mmol, 2.0 mol %), styrene (46.8 mg, 0.45 mmol), **B5** (61.6 mg, 0.30 mmol), AgSbF_6 (8.3 mg, 24 mmol, 8.0 mol %), and $\text{Cu}(\text{OAc})_2$ (108 mg, 0.60 mmol) in 1,4-dioxane (1.5 mL) was stirred at $120\text{ }^\circ\text{C}$ for 13 h. After being cooled to room temperature, 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/ethyl acetate = 10/1) and gel permeation chromatography to afford **D1** (62.8 mg, 0.204 mmol, 68%); IR (neat): 2928, 1693, 1568, 1462, 1252, 691 cm^{-1} ; ^1H NMR: $\delta = 1.50$ – 1.62 (m, 2H), 1.63– 1.85 (m, 6H), 2.60– 2.70 (m, 2H), 4.18 (t, $J = 5.2$ Hz, 2H), 6.82– 6.89 (m, 1H), 7.06 (d, $J =$

16.0 Hz, 1H), 7.10 (d, $J = 16.0$ Hz, 1H), 7.24–7.38 (m, 5H), 7.45–7.50 (m, 2H); ^{13}C NMR: $\delta = 23.8, 25.4, 26.4, 27.3, 43.8, 71.4, 112.4, 118.3, 124.5, 126.7, 127.9, 128.5, 129.9, 131.6, 131.7, 134.6, 136.8, 156.3, 209.1$; HRMS (APCI): Calcd for $\text{C}_{21}\text{H}_{23}\text{O}_2$, $[\text{M}+\text{H}]^+$ 307.1693. Found m/z 307.1682.

A mixture of **D1** (62.8 mg, 0.204 mmol) and Pd/C (10 wt. %, 12.4 mg) in anhydrous THF (5 mL) was stirred under hydrogen atmosphere (1 atm) at room temperature for 2 h. The reaction mixture was filtered through a celite pad and concentrated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 10/1) to afford **1d** (60.2 mg, 0.196 mmol, 96%); IR (neat): 2359, 1690, 1456, 1267, 1072, 694 cm^{-1} ; ^1H NMR: $\delta = 1.51\text{--}1.70$ (m, 4H), 1.71–1.87 (m, 4H), 2.48–2.55 (m, 2H), 2.76–2.84 (m, 2H), 2.85–2.92 (m, 2H), 4.15 (t, $J = 5.2$ Hz, 2H), 6.80 (d, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 7.6$ Hz, 1H), 7.11–7.30 (m, 6H); ^{13}C NMR: $\delta = 24.2, 25.2, 26.5, 27.8, 35.0, 38.2, 43.0, 71.5, 111.2, 122.6, 125.9, 128.3, 128.5, 129.9, 132.4, 139.2, 141.6, 156.6, 209.2$; HRMS (APCI): Calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2$, $[\text{M}+\text{H}]^+$ 309.1849. Found m/z 309.1841.

Synthesis of **1e**



E2 was synthesized from **B5** in the same way as **1d** from **B5**.

E1: IR (neat): 2937, 1715, 1456, 1269, 1171, 789 cm^{-1} ; ^1H NMR: $\delta = 1.51\text{--}1.84$ (m, 8H), 2.61–2.68 (m, 2H), 3.77 (s, 3H), 4.17 (t, $J = 5.2$ Hz, 2H), 6.37 (d, $J = 16.0$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.34 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.59 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR: $\delta = 23.8, 25.3, 26.5, 27.5, 43.6, 51.8, 71.7, 114.9, 119.5, 120.9, 130.3, 132.0, 133.2, 140.9, 156.6, 166.7, 207.9$; HRMS (APCI): Calcd for $\text{C}_{17}\text{H}_{21}\text{O}_4$, $[\text{M}+\text{H}]^+$ 289.1434, Found m/z 289.1427.

E2: IR (neat): 2928, 1734, 1693, 1454, 1261, 1169, 1072 cm^{-1} ; ^1H NMR: $\delta = 1.51\text{--}1.70$ (m, 4H), 1.73–1.86 (m, 4H), 2.57–2.67 (m, 4H), 2.77–2.86 (m, 2H), 3.65 (s, 3H), 4.14 (t,

$J = 5.2$ Hz, 2H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.84 (d, $J = 7.6$ Hz, 1H), 7.25 (dd, $J = 8.0$, 8.0 Hz, 1H); ^{13}C NMR: $\delta = 24.0$, 24.9, 26.4, 27.6, 27.8, 35.6, 42.6, 51.3, 71.3, 111.4, 122.1, 130.1, 132.2, 137.8, 156.5, 172.9, 208.7; HRMS (APCI): Calcd for $\text{C}_{17}\text{H}_{23}\text{O}_4$, $[\text{M}+\text{H}]^+$ 291.1591. Found m/z 291.1583.

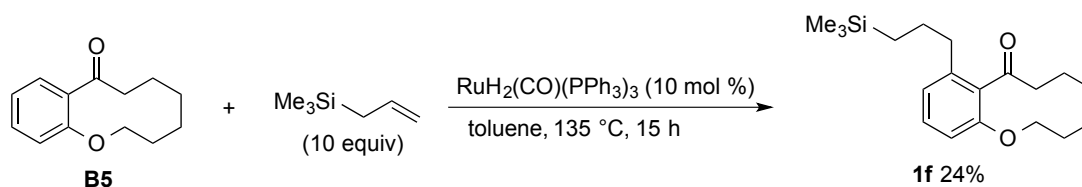
To a lithium aluminum hydride (68.4 mg, 1.8 mmol) in anhydrous THF (2.0 mL) was added dropwise **E2** (186 mg, 0.60 mmol) in anhydrous THF (1.0 mL) at 0 °C. After stirring the reaction mixture for 10 h at room temperature, ethyl acetate and water were added slowly at 0 °C. The mixture was extracted with ethyl acetate, washed with water and brine, dried over Na_2SO_4 , and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford **E3** (137 g, 0.52 mmol, 86%); IR (neat): 3296, 2930, 1452, 1252, 1030, 731 cm^{-1} ; ^1H NMR: $\delta = 1.07$ –1.37 (m, 2H), 1.40–1.55 (m, 2H), 1.59–1.91 (m, 7H), 1.92–2.05 (m, 1H), 2.59–2.71 (m, 1H), 2.86–2.99 (m, 1H), 3.26–3.50 (m, 2H), 3.52–3.66 (m, 2H), 4.07–4.18 (m, 1H), 4.25–4.38 (m, 1H), 5.46 (dd, $J = 8.0$, 4.0 Hz, 1H), 6.74 (d, $J = 8.0$ Hz, 1H), 6.80 (d, $J = 7.6$ Hz, 1H), 7.13 (dd, $J = 8.0$, 7.6 Hz, 1H); ^{13}C NMR (CD_3CN): $\delta = 23.6$, 27.2, 27.3, 28.1, 29.7, 36.1, 37.3, 62.2, 68.2, 71.9, 112.2, 124.6, 128.4, 132.8, 143.1, 158.0; HRMS (APCI): Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_3\text{Na}$, $[\text{M}+\text{Na}]^+$ 287.1618. Found m/z 287.1612.

To a sodium hydride (60 % in oil dispersion, 28.4 mg, 1.8 mmol) in anhydrous DMF (1.0 mL) was added dropwise **E3** (137 mg, 0.52 mmol) in anhydrous DMF (1.0 mL) at 0 °C. After stirring for 20 min., BnBr (120 mg, 0.70 mmol) was added to the reaction mixture. The reaction mixture was stirred for 3 h at room temperature, then water was added. The mixture was extracted with ethyl acetate, washed with water and brine, dried over Na_2SO_4 , and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to afford **E4** (70 mg, 0.20 mmol, 38%); IR (neat): 3422, 2926, 1578, 1452, 1234, 1028, 733 cm^{-1} ; ^1H NMR: $\delta = 1.18$ –2.13 (m, 12H), 2.68–2.87 (m, 2H), 3.53 (t, $J = 6.0$ Hz, 2H), 3.89 (br s, 1H), 4.05–4.15 (m, 1H), 4.36–4.45 (m, 1H), 4.51 (d, $J = 12.0$ Hz, 1H), 4.54 (d, $J = 12.0$ Hz, 1H), 5.37 (dd, $J = 6.4$, 3.6 Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 6.8$ Hz, 1H), 7.11–7.17 (m, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR: $\delta = 22.8$, 27.2, 27.35, 27.44, 29.3, 31.5, 35.6, 69.6, 70.1, 71.5, 72.8, 111.5, 123.4, 127.5, 127.56, 127.62, 128.3, 130.7, 138.5, 140.7, 157.6; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{30}\text{O}_3\text{Na}$, $[\text{M}+\text{Na}]^+$ 377.2087. Found m/z 377.2079.

To a solution of oxalyl chloride (30.4 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added dropwise DMSO (21.5 mL, 0.30 mmol) at -78 °C. After stirring for 20 min., a solution of crude **E2** (70.0 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added slowly to the mixture. The reaction mixture was stirred for 1 h at -78 °C, Et_3N (1.0 mL)

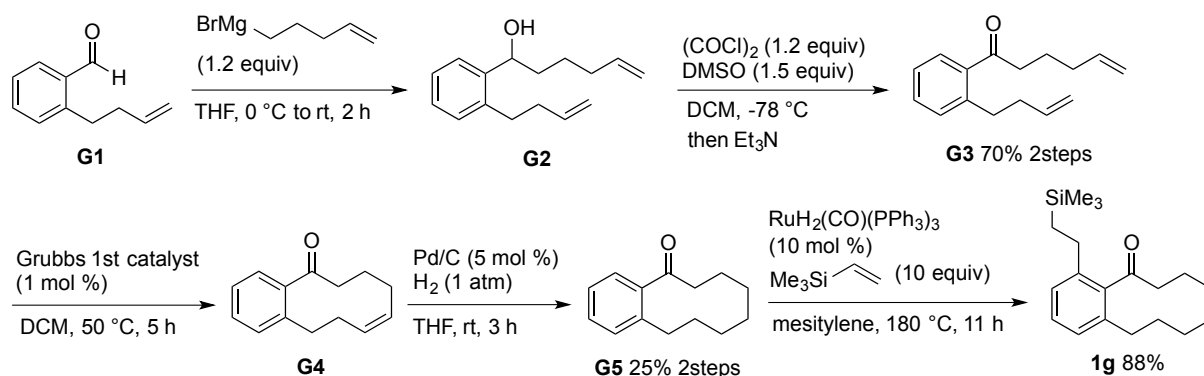
was added by syringe. After stirring at room temperature for 40 min., water was added. The mixture was extracted with CH_2Cl_2 , washed with water and brine, dried over MgSO_4 , and evaporated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 10/1) to afford **1e** (17.4 g, 0.174 mmol, 87%); IR (neat): 2928, 1693, 1454, 1261, 1090, 733 cm^{-1} ; ^1H NMR: δ = 1.50–1.70 (m, 4H), 1.73–1.83 (m, 4H), 1.84–1.95 (m, 2H), 2.54–2.67 (m, 4H), 3.48 (t, J = 6.0 Hz, 2H), 4.14 (t, J = 5.2 Hz, 2H), 4.49 (s, 2H), 6.78 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 7.19–7.37 (m, 6H); ^{13}C NMR: δ = 24.1, 25.3, 26.5, 27.7, 29.2, 31.5, 43.2, 69.5, 71.5, 72.8, 111.1, 122.5, 127.5, 127.7, 128.3, 129.8, 132.5, 138.5, 139.4, 156.4, 209.3; HRMS (APCI): Calcd for $\text{C}_{23}\text{H}_{29}\text{O}_3$, $[\text{M}+\text{H}]^+$ 353.2111. Found m/z 353.2104.

Synthesis of **1f**



1f was synthesized from **B5** in the same way as **1b** from **B5**. Allyltrimethylsilane was employed instead of vinyl trimethylsilane. 24% yield; IR (neat): 2928, 1695, 1246, 833 cm^{-1} ; ^1H NMR: δ = -0.04 (s, 9H), 0.45–0.55 (m, 2H), 1.48–1.70 (m, 6H), 1.71–1.86 (m, 4H), 2.51 (t, J = 7.6 Hz, 2H), 2.56–2.65 (m, 2H), 4.14 (t, J = 5.2 Hz, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 7.23 (dd, J = 8.0, 7.6 Hz, 1H); ^{13}C NMR: δ = -1.7, 16.8, 24.2, 25.3, 26.4, 26.5, 27.8, 36.6, 43.3, 71.5, 110.9, 122.5, 129.7, 132.4, 140.2, 156.4, 209.3; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{31}\text{O}_2\text{Si}$, $[\text{M}+\text{H}]^+$ 319.2088. Found m/z 319.2080.

Synthesis of **1g**



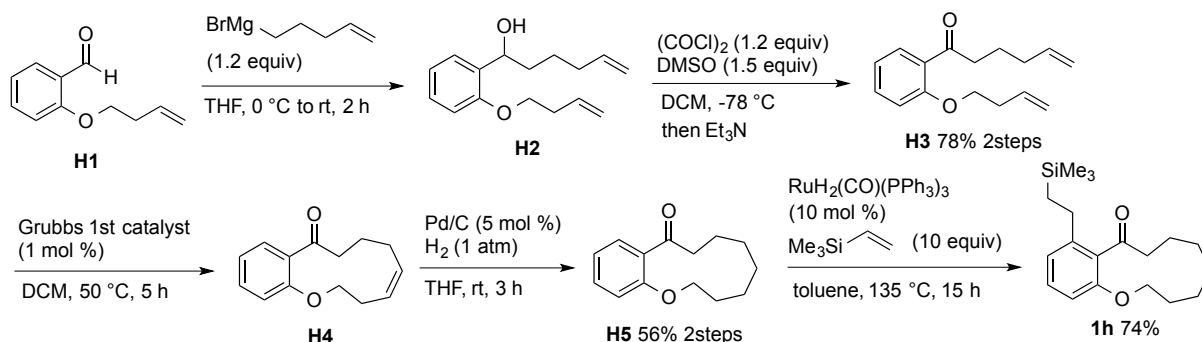
G5 was synthesized from **G1** in the same way with **B5** from **B1**. The spectroscopic

data of **G5** was identical to the reported values.¹⁹

G3: IR (neat): 2934, 1684, 993, 908, 752 cm^{-1} ; ^1H NMR: δ = 1.82 (tt, J = 7.2, 7.2 Hz, 2H), 2.10–2.19 (m, 2H), 2.29–2.38 (m, 2H), 2.85–2.92 (m, 4H), 4.92–5.07 (m, 4H), 5.73–5.92 (m, 2H), 7.23–7.28 (m, 2H), 7.38 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.56 (dd, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR: δ = 23.3, 33.1, 33.3, 35.8, 41.2, 114.9, 115.3, 125.8, 128.1, 130.9, 131.1, 138.0, 138.1, 138.6, 141.3, 204.8; HRMS (APCI): Calcd for $\text{C}_{16}\text{H}_{21}\text{O}$, $[\text{M}+\text{H}]^+$ 229.1587. Found m/z 229.1582.

A mixture containing $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ (36.6 mg, 0.040 mmol, 10 mol %), vinyltrimethylsilane (400 mg, 4.0 mmol), and **G5** (80.8 mg, 0.40 mmol) in mesitylene (0.60 mL) was stirred at 180 °C for 11 h. After being cooled to room temperature, the reaction mixture was passed through a pad of Florisil[®], eluted with ethyl acetate and evaporated. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford **1g** (105.7 mg, 0.35 mmol, 88%); IR (neat): 2930, 1684, 1246, 829 cm^{-1} ; ^1H NMR (C_6D_6): δ = -0.08 (s, 9H), 0.70–0.81 (m, 2H), 0.96–1.10 (m, 2H), 1.15–1.31 (m, 4H), 1.40–1.52 (m, 2H), 1.62–1.84 (m, 2H), 2.44–2.56 (m, 2H), 2.59–2.97 (m, 4H), 6.89–6.94 (m, 2H), 7.09 (dd, J = 7.6, 7.6 Hz, 1H); ^{13}C NMR: δ = -1.9, 18.9, 22.5, 22.6, 23.5, 27.9, 28.5, 28.6, 29.6, 45.4, 126.2, 127.7, 129.0, 138.8, 139.5, 142.0, 212.2; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{31}\text{OSi}$, $[\text{M}+\text{H}]^+$ 303.2139. Found m/z 303.2132.

Synthesis of **1h**



1h was synthesized from **H1** in the same way as **1b** from **B1**.

H3: IR (neat): 2924, 1668, 1595, 1448, 1238, 901, 750 cm^{-1} ; ^1H NMR: δ = 1.78 (tt, J = 7.2, 7.2 Hz, 2H), 2.07–2.15 (m, 2H), 2.60 (dtdd, J = 6.8, 6.4, 1.2, 1.2 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 4.11 (t, J = 6.4 Hz, 2H), 4.96 (ddt, J = 10.4, 2.4, 1.2 Hz, 1H), 5.02 (ddt, J = 16.8, 1.6, 1.6 Hz, 1H), 5.13 (ddt, J = 10.4, 1.6, 1.6 Hz, 1H), 5.19 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H), 5.81 (ddt, J = 16.8, 10.0, 6.4 Hz, 1H), 5.90 (ddt, J = 16.8, 10.4, 6.8 Hz, 1H),

6.93 (d, $J = 8.4$ Hz, 1H), 6.98 (ddd, $J = 7.2, 7.2, 0.8$ Hz, 1H), 7.42 (ddd, $J = 8.4, 7.2, 2.0$ Hz, 1H), 7.66 (dd, $J = 7.6, 2.0$ Hz, 1H); ^{13}C NMR: $\delta = 23.5, 33.3, 33.6, 43.3, 67.6, 112.1, 114.8, 117.4, 120.6, 128.7, 130.2, 133.1, 134.3, 138.4, 157.7, 202.9$; HRMS (APCI) Calcd for $\text{C}_{16}\text{H}_{21}\text{O}_2$, $[\text{M}+\text{H}]^+$ 245.1536, found 245.1532.

H5: IR (neat): 2928, 1668, 1595, 1447, 1242, 1011, 750 cm^{-1} ; ^1H NMR: $\delta = 1.46\text{--}1.69$ (m, 6H), 1.78–1.97 (m, 4H), 2.83 (t, $J = 6.4$ Hz, 2H), 4.13 (t, $J = 5.2$ Hz, 2H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.93–6.99 (m, 1H), 7.35–7.42 (m, 1H), 7.44 (dd, $J = 7.6, 2.0$ Hz, 1H); ^{13}C NMR: $\delta = 24.3, 24.9, 25.1, 25.8, 26.4, 40.8, 69.6, 112.0, 120.4, 128.5, 131.2, 132.3, 157.3, 207.0$; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 219.1380. Found m/z 219.1374.

1h: IR (neat): 2924, 1697, 1578, 1447, 1254, 831 cm^{-1} ; ^1H NMR: $\delta = 0.00$ (s, 9H), 0.74–0.87 (m, 2H), 1.42–1.68 (m, 6H), 1.79–1.92 (m, 4H), 2.39–2.49 (m, 2H), 2.68–2.75 (m, 2H), 3.98 (t, $J = 4.8$ Hz, 2H), 6.63 (d, $J = 8.4$ Hz, 1H), 6.79 (d, $J = 7.6$ Hz, 1H), 7.20 (dd, $J = 8.0, 8.0$ Hz, 1H); ^{13}C NMR: $\delta = -1.9, 19.5, 22.7, 23.5, 24.4, 24.9, 26.3, 26.9, 41.5, 68.4, 107.6, 120.5, 129.6, 131.9, 142.2, 155.5, 209.8$; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{31}\text{O}_2\text{Si}$, $[\text{M}+\text{H}]^+$ 319.2088. Found m/z 319.2080.

Computational study

All calculations were performed with Gaussian 09 software package²⁰. The density functional theory (DFT) method with the B3LYP (Becke's three-parameter hybrid functional²¹, LYP correlation functional²²) functional was utilized to fully optimize all the stationary points on the potential energy surface (PES) without symmetry and geometric constraints, in conjunction with at the 6-31G(d) basis set. Zero-point energy, enthalpy, and Gibbs free energy at 298.15 K and 1 atm were estimated from the gas-phase studies. Harmonic vibration frequency calculations at the same level were performed to verify all stationary points have no imaginary frequency.

Uncorrected and thermal corrected energies of stationary points (Unit: Hartree)

Compounds	E	H	G
1a	-694.770459538	-694.460430	-694.517544
5a	-694.721890354	-694.411860	-694.466033
2a	-694.766500280	-694.455955	-694.511412

E: electronic energy, H: sum of electronic and thermal enthalpies, G: sum of electronic and thermal free energies

Cartesian coordinates of optimized structures

1a

O	-0.656361	-2.049748	1.576790
C	-0.496099	-1.498392	0.503382
C	-1.197019	-0.185460	0.195531
C	-3.382204	-1.437120	-0.127782
C	-0.471012	1.015039	0.248626
C	-2.568015	-0.162298	-0.113607
H	-3.343749	-1.939335	0.844449
H	-4.429012	-1.228475	-0.366932
C	-1.077748	2.235495	-0.061386
C	-3.169064	1.066623	-0.416709
C	-2.430786	2.248240	-0.398452
H	-0.511780	3.159970	-0.021199
H	-4.226047	1.092304	-0.668373
H	-2.913108	3.192322	-0.637563
C	0.312561	-2.154579	-0.616079
H	-0.394240	-2.349760	-1.437171
H	0.652905	-3.124104	-0.235014
C	1.495271	-1.336585	-1.169423
H	1.836949	-1.811356	-2.098601
H	1.137084	-0.344248	-1.460303
C	2.683327	-1.228184	-0.190466
H	3.301205	-2.128988	-0.300489
H	2.316905	-1.238167	0.841982
C	3.565884	0.022817	-0.401482
C	1.798572	1.846834	0.202506
H	1.685842	2.783415	0.766704
H	1.633806	2.070502	-0.861667
H	3.575521	0.292709	-1.468012
H	4.605192	-0.223287	-0.148780
C	3.185265	1.257608	0.439015

Chapter 4

H	3.268208	1.010713	1.505739
H	3.914095	2.057039	0.247296
H	-3.009040	-2.152427	-0.872419
O	0.832068	0.892365	0.649249

5a

O	-0.387738	-2.093393	1.521739
C	-0.858479	-1.568136	0.288507
C	-1.114960	-0.064430	0.224027
C	-2.429068	-1.721107	0.012283
C	-0.484603	1.172325	0.312966
C	-2.454067	-0.202465	-0.121496
H	-2.967892	-2.113627	0.882486
H	-2.710764	-2.309068	-0.868955
C	-1.265035	2.293433	-0.015575
C	-3.243199	0.893025	-0.454468
C	-2.608777	2.144309	-0.395185
H	-0.829175	3.287332	0.036919
H	-4.287010	0.811612	-0.744613
H	-3.176650	3.038944	-0.639513
C	0.045518	-2.141395	-0.820327
H	-0.549356	-2.231690	-1.737415
H	0.318461	-3.160865	-0.517927
C	1.298872	-1.315858	-1.160012
H	1.757881	-1.750924	-2.059652
H	0.968702	-0.314187	-1.461377
C	2.380644	-1.203354	-0.069481
C	3.405380	-0.079628	-0.364318
C	1.794523	1.954532	0.025705
H	1.809090	2.998721	0.369568
H	1.543979	1.954096	-1.043711
H	3.489846	0.054561	-1.453280

Chapter 4

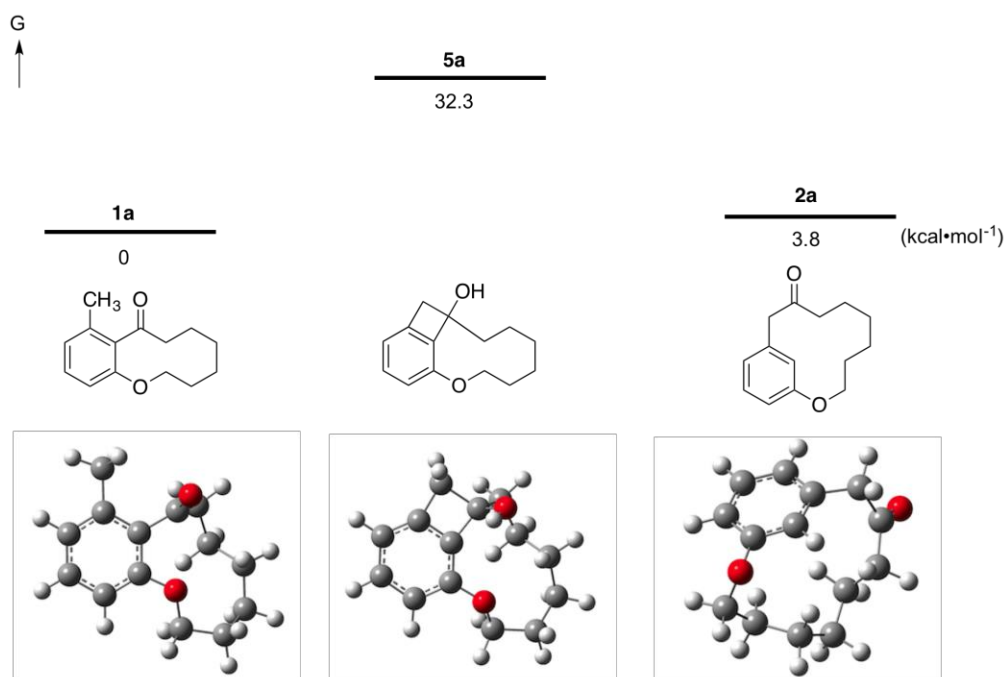
H	4.401328	-0.399467	-0.031083
C	3.145439	1.292684	0.293539
H	-0.788836	-1.571351	2.235109
O	0.805745	1.218327	0.759129
H	1.918547	-1.045327	0.907888
H	2.907328	-2.165262	-0.007302
H	3.928347	1.990877	-0.034153
H	3.248991	1.202541	1.383078

2a

O	-3.680246	0.455550	0.527749
C	-2.723989	0.365118	-0.217220
C	0.129287	-0.994140	-1.041792
C	-2.389759	-0.970283	-0.916397
C	1.379342	-1.257225	-0.482099
C	-1.040699	-1.494550	-0.463695
H	-2.385381	-0.799482	-2.001583
H	-3.195169	-1.669754	-0.677679
C	1.488836	-2.138929	0.598403
C	-0.930276	-2.360705	0.633123
C	0.327761	-2.697821	1.136643
H	2.463469	-2.372739	1.016123
H	-1.827854	-2.758497	1.098996
H	0.404571	-3.384718	1.975409
C	-1.800475	1.559432	-0.460980
H	-2.436471	2.427561	-0.671941
H	-1.173462	1.387932	-1.340279
C	-0.921751	1.866462	0.778151
H	-1.571579	2.286991	1.553682
H	-0.529168	0.929579	1.189770
C	0.244990	2.834414	0.488439
H	-0.133867	3.686290	-0.092893

H	0.598119	3.253388	1.441300
C	1.446800	2.208748	-0.252383
C	3.178112	0.276107	-0.131825
H	3.884014	0.798487	-0.785064
H	3.762745	-0.320050	0.583272
H	2.091417	3.012027	-0.633518
H	1.095145	1.665767	-1.136085
C	2.287995	1.265713	0.629383
H	2.942776	1.856386	1.285391
H	1.634543	0.694274	1.298561
H	0.087549	-0.335132	-1.902879
O	2.459192	-0.597094	-1.026136

Figure 1. Energy diagram of constitutional isomers **1a**, **5a**, and **2a**



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Chapter 5

Ring Opening of Alkoxybenzocyclobutenes with Site-Selective Hydrogenolysis of C(sp²)–C(sp³) Bond

Abstract

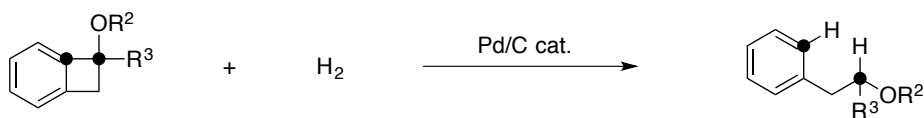
1-Alkoxybenzocyclobutenes undergo ring-opening hydrogenolysis by a palladium on carbon catalyst. The proximal C(sp²)–C(sp³) bond is site-selectively cleaved and hydrogenated in preference to the benzylic carbon–oxygen bond and the thermally labile the distal C(sp³)–C(sp³) bond.

Introduction

Hydrogenation is one of the fundamental reactions frequently utilized in organic synthesis.¹ A palladium catalyst shows the high catalytic activity towards the reduction of various unsaturated functionalities such as alkenes, alkynes, arenes, carbonyl compounds, and nitrogen-containing multiple bonds.² Moreover, hydrogenolysis of a benzylic carbon–oxygen bond can also be performed in the presence of a palladium catalyst to deliver the corresponding alcohol and toluene.³ In addition to these typical reactions of functional groups, hydrogenolysis of carbon–carbon (C–C) σ -bonds has also been reported.⁴ Not only small cycloalkanes⁵ but also unstrained α -benzyl Meldrum's acid^{4e} undergo hydrogenolysis of the C–C σ -bond.

As shown in previous chapters, the author has found that a rhodium catalyst induced ring opening of benzocyclobutenols with site-selective cleavage of the proximal C(sp²)–C(sp³) bonds.⁶ In the course of these studies, the author found that a palladium on charcoal catalyst showed the catalytic activity to cleave the proximal C(sp²)–C(sp³) bond of alkoxybenzocyclobutenes under hydrogen atmosphere.⁷ The proximal C(sp²)–C(sp³) bond is selectively cleaved in preference to the seemingly more reactive benzylic C–O bond and the thermally labile C(sp³)–C(sp³) bond.

Scheme 1. Hydrogenolysis of 1-alkoxybenzocyclobutenes with site-selectivity

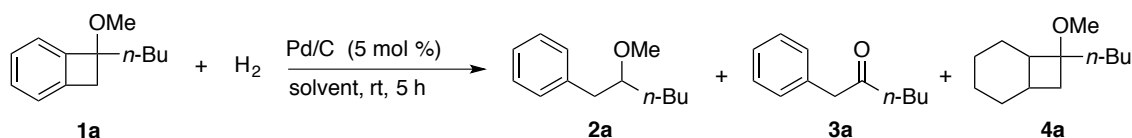


Results and Discussions

Initially, the author optimized the reaction conditions (Table 1). When 1-methoxybenzocyclobutene **1a** was stirred in the presence of a catalytic amount of Pd/C under atmospheric hydrogen in methanol, ring-opening product **2a** was obtained in 5% yield with the generation of benzyl butyl ketone **3a** and a trace amount of **4a** (entry 1).⁸ Similarly, the toluene solution of **1a** didn't proceed the reaction completely to recover the starting material **1a** (entry 2). In contrast, when ethyl acetate was employed as a solvent, the starting material **1a** was consumed to afford **2a** in moderate yield (entry 3). Dichloromethane improved the selectivity to reduce the formation of **3a** (entry 4). When molecular sieves 4A was added to the reaction system, the formation of

benzyl butyl ketone **3a** was suppressed to afford the target compound **2a** in 82% isolated yield with a trace amount of **4a** (entry 5). There was no product derived from hydrogenolysis of the benzylic C–O bond and the other C–C bonds including the thermally labile C(sp³)–C(sp³) bond and the sterically less-hindered C(sp²)–C(sp³) bond.

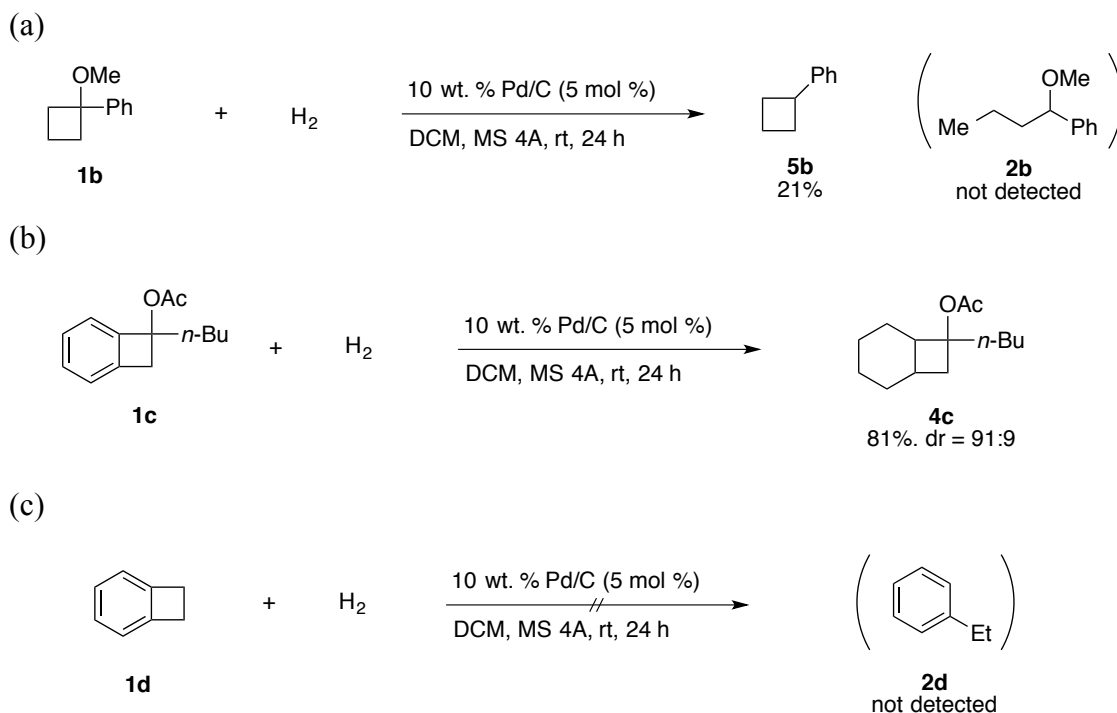
Table 1. Optimization of reaction conditions^a



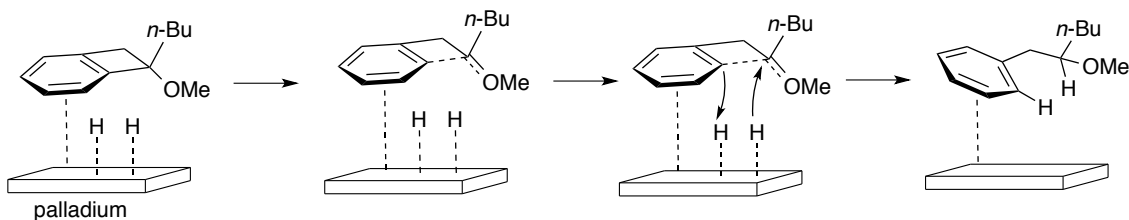
entry	solvent	additive	2a /% ^b	3a /% ^b	4a /% ^b
1	MeOH	–	5	21	trace
2	AcOEt	–	65	35	trace
3	toluene	–	7	1	trace
4	DCM	–	69	13	trace
5	DCM	MS 4A	82 ^c	0	trace

^a Reaction conditions: methoxybenzocyclobutene **1a** (0.20 mmol), metal catalyst (5 mol %) and solvent (3.0 mL) were stirred under hydrogen for 5 h at room temperature. ^b NMR yield. ^c Isolated yield.

To obtain the mechanistic insight, the author conducted following experiments. When methoxycyclobutane **1b** was subjected to the identical reaction conditions, the benzylic C–O bond was cleaved to afford the product **5b** in 21% yield with the recovery of starting material **1b** in 52% yield. However, C–C bond cleavage product **2b** was not detected, indicating that the fused benzene ring facilitates hydrogenolysis of C–C bond (Scheme 2a). Replacement of the methoxy group of **1a** with an acetoxy group completely suppress the hydrogenolysis of the C(sp²)–C(sp³) bond and instead reduction of the benzene ring took place to give **4c** in 81% isolated yield (Scheme 2b). Moreover, hydrogenation of simple benzocyclobutene **1d** also failed to give ethylbenzene **2d** (Scheme 2c). The reduction of benzene ring took place to afford some saturated compound. These results suggest that an electron-donating nature of the oxygen atom accelerates the hydrogenolysis of the C(sp²)–C(sp³) bond.

Scheme 2. Mechanistic studies

Based on these experimental results, the author tentatively assumes **2a** is produced from **1a** through the mechanistic scenario as follows. Initially, dihydrogen is split into two hydrogen atoms on the surface of Pd/C.⁹ The benzene ring of the benzocyclobutene **1a** is adsorbed on Pd/C, which induces cleavage of the proximal C(sp²)-C(sp³) bond with assistance of electron donation from the lone pair of electrons on oxygen. Hydride is transferred to the oxocarbenium-type carbon to form carbon-hydrogen bond with the formation of C(sp²)-H bond to afford the product **2a**.¹⁰

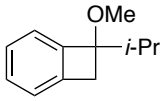
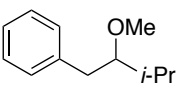
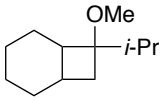
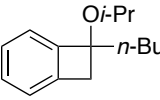
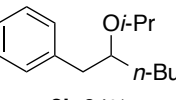
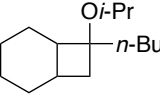
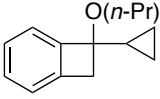
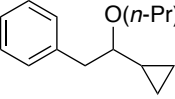
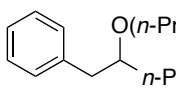
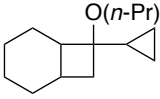
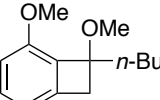
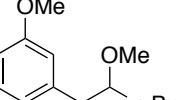
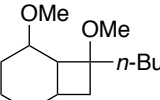
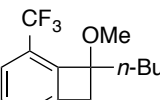
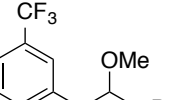
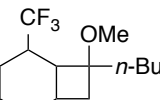
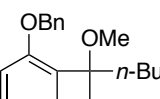
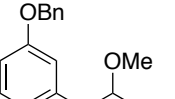
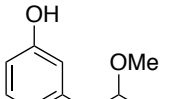
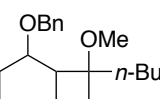
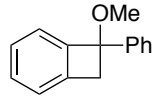
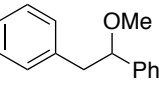
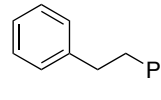
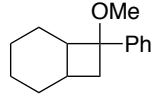
Scheme 3. A possible reaction mechanism

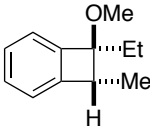
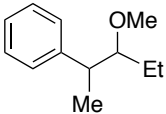
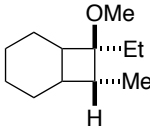
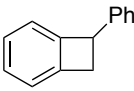
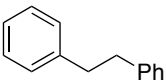
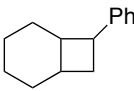
The scope of the present hydrogenolysis is summarized in Table 2. The secondary benzocyclobutenyl ethers **1e** and **1f** underwent hydrogenolysis of the C-C σ -bond to give the ring-opening products **2e** and **2f** together with the arene-hydrogenated products **3e** and **3f** (entries 1 and 2). Reaction of the isopropyl-substituted benzocyclobutene **1g**

afforded ring-opening product **2g** selectively (entry 3). The isopropyl ether **1h** underwent efficient hydrogenolysis of the C–C σ -bond to give **2h** exclusively. Although cyclopropyl group substituted substrate **1i** also gave the C–C bond cleavage product **2i** in 25% yield, hydrogenolysis of cyclopropane moiety was competed to generate **2i'** (entry 5).⁵ Whereas introduction of a methoxy group at the 6-position of benzocyclobutene ring accelerated hydrogenation of the arene ring, introduction of trifluoromethyl group at the same position reduced the amount of the arene-hydrogenated product (entries 6 and 7). The substrate bearing benzyl ether moiety **1l** could be applied for this reaction. Hydrogenolysis of the C–C bond took place more rapidly than that of the benzylic C–O bond (entry 8). The reaction of methoxybenzocyclobutene possessing a phenyl group at R³ position **1m** gave the corresponding product **2m** in 21% yield with the generation of bibenzyl **2m'** (entry 9). When methoxybenzocyclobutene as a single diastereomer **1n** was utilized to this reaction condition, the corresponding product **2n** was obtained in 75% yield as a diastereo mixture (dr = 68:32) (entry 10). 1-Phenyl-substituted benzocyclobutene **1q** underwent hydrogenolysis very slowly to afford **2q** (entry 13).

Table 2. Scope of substrates^a

entry	1	2^b	3^b
1	 1e	 2e 65%	 3e <17%
2	 1f	 2f 28%	 3f 51%

entry	1	2^b	3^b
3	 1g	 2g 77%	 3g trace
4	 1h	 2h 94%	 3h not detected
5	 1i	 2i 25% +  2i' 50%	 3i trace
6	 1j	 2j 69%	 3j 19%
7	 1k	 2k 87%	 3k not detected
8	 1l	 2l 70% +  2l' 17%	 3l trace
9	 1m	 2m 21% +  2m' 25%	 3m 18%

entry	1	2^b	3^b
10	 1n	 2n 75% dr = 68:32	 3n trace
11	 1q	 2q 18%	 3m trace

^a Reaction conditions: alkoxybenzocyclobutene **1** (0.20 mmol), palladium on carbon (5 mol % Pd), MS 4A (20.0 mg), dichloromethane (3.0 mL), rt, 24 h unless otherwise noted. ^b Isolated yields. ^c Palladium on carbon (10 mol % Pd), MS 4A (30.0 mg) ^dNMR yield. ^e The reaction was performed in MeOH without MS 4A.

Conclusions

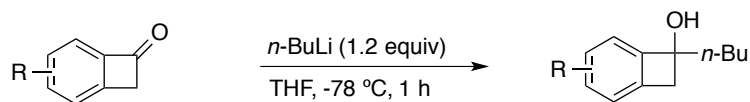
1-alkoxybenzocyclobutenes undergo hydrogenolysis with site-selective cleavage of the sterically more hindered C(sp²)–C(sp³) bond. The benzylic C–O σ -bond and the other C(sp³)–C(sp³) bonds including sterically more accessible ones remain intact under the present reaction conditions.

Experimental section

General. All reactions were carried out in oven-dried glassware with standard Schlenk techniques unless otherwise noted. 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). Gel permeation chromatography was carried out with a Japan Analytical Industry LC-9210II NEXT.

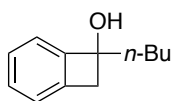
Materials. Anhydrous DCM and THF were purchased from Kanto Chemical Co. The following compounds were synthesized according to the literature procedures; benzocyclobutenone,^{11a} methoxybenzocyclobutenone,^{11a} 6-trifluoromethylbenzocyclobutenone,^{11b} 6-benzyloxybenzocyclobutenone,^{11c} 2-ethyl-1-methylbenzocyclobutenol,^{11d} 1-*tert*-butyldimethylsiloxybenzocyclobutene **1d**,^{11e} and 1-phenylbenzocyclobutene **1k**^{11d}. All other commercially available chemical resources were used as received without further purification.

General procedure for the synthesis of benzocyclobutenols



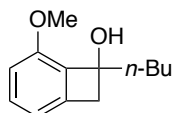
To a stirred solution of benzocyclobutenone (1.0 equiv) in THF (3 mL/mmol) was added *n*-BuLi (hexane solution, 1.6 M, 1.2 equiv) slowly at $-78\text{ }^\circ\text{C}$. After stirring for 1 h at $-78\text{ }^\circ\text{C}$, saturated NH_4Cl aq was added. The mixture was extracted with Et_2O , washed with water and brine, dried over MgSO_4 and evaporated. After purification by chromatography on silica gel, the corresponding benzocyclobutenol was obtained.

S1:

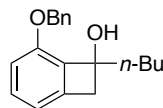


Purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1); Yield

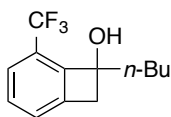
80%; IR (neat): 3333, 2955, 1457, 1165, 714 cm^{-1} ; ^1H NMR: δ = 0.92 (t, J = 7.6 Hz, 3H), 1.30–1.42 (m, 2H), 1.47–1.59 (m, 2H), 1.81–1.97 (m, 2H), 2.23 (br s, 1H), 3.15 (d, J = 14.0 Hz, 1H), 3.36 (d, J = 14.0 Hz, 1H), 7.14–7.31 (m, 4H); ^{13}C NMR: δ = 14.1, 23.0, 27.1, 38.8, 46.9, 81.0, 121.1, 124.0, 127.1, 129.2, 141.5, 150.4; HRMS (APCI): Calcd for $\text{C}_{12}\text{H}_{17}\text{O}$, $[\text{M}+\text{H}]^+$ 177.1274. Found m/z 177.1271.

S2:

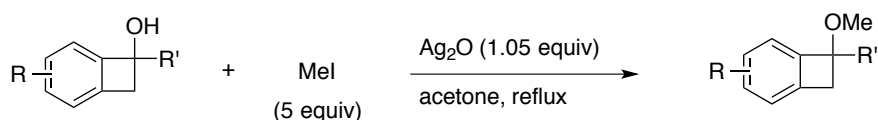
Purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1); Yield 92%; IR (neat): 3196, 2932, 1475, 1266, 1043, 773 cm^{-1} ; ^1H NMR: δ = 0.91 (t, J = 6.8 Hz, 2H), 1.30–1.43 (m, 3H), 1.45–1.59 (m, 1H), 1.83–1.92 (m, 1H), 1.96–2.07 (m, 1H), 2.50 (br s, 1H), 3.60 (d, J = 14.0 Hz, 1H), 3.32 (d, J = 14.0 Hz, 1H), 3.87 (s, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 7.2 Hz, 1H), 7.22 (dd, J = 8.4, 7.2 Hz, 1H); ^{13}C NMR: δ = 14.0, 23.0, 39.2, 45.7, 56.3, 80.6, 112.0, 116.0, 130.8, 134.5, 143.2, 153.7; HRMS (APCI): Calcd for $\text{C}_{13}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 207.1380. Found m/z 207.1377.

S3:

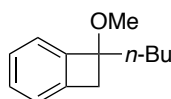
Purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1); Yield 83%; IR (neat): 3342, 2966, 1464, 1261, 1051, 731 cm^{-1} ; ^1H NMR: δ = 0.90 (t, J = 7.2 Hz, 3H), 1.30–1.46 (m, 3H), 1.49–1.64 (m, 1H), 1.86–1.96 (m, 1H), 1.98–2.08 (m, 1H), 2.34 (br s, 1H), 3.08 (d, J = 14.0 Hz, 1H), 3.34 (d, J = 14.4 Hz, 1H), 5.15 (d, J = 12.0 Hz, 1H), 5.22 (d, J = 11.6 Hz, 1H), 6.75–6.80 (m, 2H), 7.21 (dd, J = 8.4, 7.2 Hz, 1H), 7.29–7.34 (m, 1H), 7.35–7.40 (m, 2H), 7.41–7.46 (m, 2H); ^{13}C NMR: δ = 14.1, 23.0, 27.3, 39.3, 45.8, 70.9, 80.7, 113.3, 116.4, 127.3, 127.8, 128.5, 130.8, 134.8, 137.2, 143.3, 152.9; HRMS (APCI): Calcd for $\text{C}_{19}\text{H}_{23}\text{O}_2$, $[\text{M}+\text{H}]^+$ 283.1693. Found m/z 283.1685.

S4:

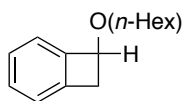
Purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1); Yield 93%; IR (neat): 3360, 2959, 1435, 1323, 1119, 783 cm^{-1} ; ^1H NMR: δ = 0.90 (t, J = 7.2 Hz, 3H), 1.16–1.56 (m, 4H), 1.85 (ddd, J = 13.6, 11.6, 4.4 Hz, 1H), 2.06 (ddd, J = 13.2, 13.2, 4.4 Hz, 1H), 2.31 (br s, 1H), 3.19 (d, J = 14.4 Hz, 1H), 3.43 (d, J = 14.4 Hz, 1H), 7.30–7.44 (m, 5H); ^{13}C NMR: δ = 14.0, 22.9, 26.7, 38.2, 44.8, 81.0, 123.5 (q, J = 270.1 Hz), 123.7 (q, J = 4.4 Hz), 124.1 (q, J = 34.4 Hz), 127.3, 129.4, 142.5, 147.5 (q, J = 2.2 Hz); HRMS (EI): Calcd for $\text{C}_{13}\text{H}_{15}\text{OF}_3$, $[\text{M}]^+$ 244.1075. Found m/z 244.1070.

General procedure for the synthesis of alkoxybenzocyclobutene

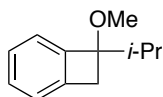
A mixture containing benzocyclobutenol (1.0 equiv), Ag_2O (1.05 equiv), MeI (5.0 equiv) and acetone (1 ml/mmol of benzocyclobutenol) was stirred at 65 $^\circ\text{C}$ under air. The reaction mixture was filtered through a celite pad and concentrated. The residue was purified by column chromatography on silica gel or gel permeation chromatography to yield methoxybenzocyclobutene.

1a:

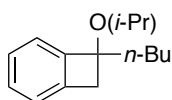
Purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1); Yield 36%; IR (neat): 2930, 1456, 1088, 752, 716 cm^{-1} ; ^1H NMR: δ = 0.91 (t, J = 8.4 Hz, 3H), 1.29–1.40 (m, 2H), 1.41–1.53 (m, 2H), 1.80–1.94 (m, 2H), 3.08 (d, J = 14.0 Hz, 1H), 3.29 (s, 3H), 3.36 (d, J = 14.0 Hz, 1H), 7.12–7.32 (m, 4H); ^{13}C NMR: δ = 14.1, 23.0, 26.9, 37.2, 40.7, 52.1, 85.8, 122.3, 123.6, 126.7, 129.0, 141.6, 148.1; HRMS (APCI): Calcd for $\text{C}_{13}\text{H}_{19}\text{O}$, $[\text{M}+\text{H}]^+$ 191.1430. Found m/z 191.1426.

1e:

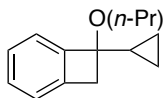
n-Hexyl iodide was employed instead of methyl iodide; Yield 23%; Purified by column chromatography on silica gel (hexane/ethyl acetate = 30/1); IR (neat): 2928, 1456, 1119, 739 cm^{-1} ; ^1H NMR: δ = 0.86–0.94 (m, 3H), 1.24–1.44 (m, 6H), 1.60–1.70 (m, 2H), 3.12 (d, J = 14.0 Hz, 1H), 3.46 (dd, J = 14.0, 4.0 Hz, 1H), 3.54–3.69 (m, 2H), 5.02–5.06 (m, 1H), 7.12–7.17 (m, 1H), 7.20–7.32 (m, 3H); ^{13}C NMR: δ = 14.0, 22.6, 25.9, 29.9, 31.7, 38.6, 69.0, 76.7, 122.7, 123.5, 126.9, 129.2, 142.6, 146.3; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{21}\text{O}$, $[\text{M}+\text{H}]^+$ 205.1587. Found m/z 205.1586.

1g:

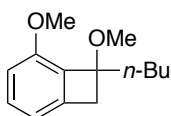
Purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1); Yield 18%; IR (neat): 2961, 1456, 1213, 1092, 750 cm^{-1} ; ^1H NMR: δ = 0.97 (d, J = 10.8 Hz, 3H), 1.51 (d, J = 10.8 Hz, 3H), 2.06 (qq, J = 6.8, 6.8 Hz, 1H), 3.13 (d, J = 14.8 Hz, 1H), 3.25 (s, 3H), 3.28 (d, J = 14.4 Hz, 1H), 7.11–7.30 (m, 4H); ^{13}C NMR: δ = 17.2, 17.6, 34.7, 38.0, 52.1, 89.2, 123.1, 123.3, 126.6, 129.0, 142.1, 147.4; HRMS (APCI): Calcd for $\text{C}_{12}\text{H}_{17}\text{O}$, $[\text{M}+\text{H}]^+$ 177.1274. Found m/z 177.1271.

1h:

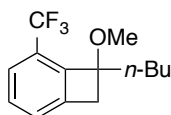
2-Propyl iodide was employed instead of methyl iodide; Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 20/1); Yield 25%; IR (neat): 2964, 1456, 1111, 754 cm^{-1} ; ^1H NMR: δ = 0.89 (d, J = 10.8 Hz, 3H), 1.12 (d, J = 5.6 Hz, 3H), 1.13 (d, J = 5.2 Hz, 3H), 1.24–1.36 (m, 2H), 1.40–1.52 (m, 2H), 3.13 (d, J = 14.4 Hz, 1H), 3.25 (d, J = 14.0 Hz, 1H), 3.62–3.73 (m, 1H), 7.13 (d, J = 6.8 Hz, 1H), 7.17–7.30 (m, 3H); ^{13}C NMR: δ = 14.1, 23.0, 24.2, 24.6, 27.1, 39.1, 43.1, 66.5, 84.9, 122.4, 123.5, 126.6, 128.8, 141.7, 149.5; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{23}\text{O}$, $[\text{M}+\text{H}]^+$ 219.1743. Found m/z 219.1740.

1i:

n-Propyl iodide was employed instead of methyl iodide; Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) and gel permeation chromatography; Yield 30%; IR (neat): 2926, 1456, 1078, 750, 715 cm^{-1} ; ^1H NMR: δ = -0.20–0.12 (m, 1H), 0.32–0.42 (m, 1H), 0.44–0.52 (m, 1H), 0.54–0.62 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H), 1.35–1.42 (m, 1H), 1.54–1.64 (m, 2H), 3.17 (d, J = 14.4 Hz, 1H), 3.30 (d, J = 14.0 Hz, 1H), 3.46 (ddd, J = 8.8, 6.8, 6.8 Hz, 1H), 3.51 (ddd, J = 8.8, 6.8, 6.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.13 (ddd, J = 6.0, 0.8, 0.8 Hz, 1H), 7.18 (dd, J = 7.2, 0.8 Hz, 1H), 7.26 (ddd, J = 7.6, 0.8, 0.8 Hz, 1H); ^{13}C NMR: δ = 0.71, 2.6, 10.7, 16.7, 23.5, 41.7, 66.7, 86.3, 122.2, 123.3, 126.5, 129.1, 142.3, 145.6; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{19}\text{O}$, $[\text{M}+\text{H}]^+$ 203.1430. Found m/z 203.1427.

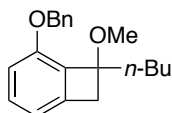
1j:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 10/1); Yield 52%; IR (neat): 2932, 1477, 1265, 1072, 766 cm^{-1} ; ^1H NMR: δ = 0.89 (t, J = 7.2 Hz, 3H), 1.22–1.56 (m, 4H), 1.78–1.88 (m, 2H), 1.96–2.08 (m, 2H), 3.03 (d, J = 14.0 Hz, 1H), 3.29 (d, J = 14.4 Hz, 1H), 3.32 (s, 3H), 3.84 (s, 3H), 6.71 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 7.2 Hz, 1H), 7.23 (dd, J = 8.4, 7.2 Hz, 1H); ^{13}C NMR: δ = 14.1, 23.0, 27.0, 38.1, 39.3, 52.1, 56.0, 85.8, 111.3, 115.9, 130.8, 132.4, 143.4, 154.5; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{21}\text{O}_2$, $[\text{M}+\text{H}]^+$ 221.1536. Found m/z 221.1532.

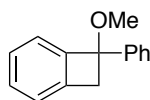
1k:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 20/1); Yield 23%; IR (neat): 2936, 1323, 1119, 783 cm^{-1} ; ^1H NMR: δ = 0.88 (t, J = 7.2 Hz, 3H), 1.08–1.22 (m, 1H), 1.23–1.52 (m, 3H), 1.78 (ddd, J = 12.0, 12.0, 4.4 Hz, 1H), 2.08 (ddd, J = 12.8, 12.8, 4.4 Hz, 1H), 3.17 (d, J = 14.8 Hz, 1H), 3.24 (s, 3H), 3.45 (d, J =

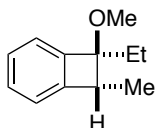
14.4 Hz, 1H), 7.21 (d, $J = 7.2$ Hz, 1H), 7.35–7.46 (m, 2H); ^{13}C NMR: $\delta = 14.0, 23.0, 26.8, 37.7, 38.6, 51.9, 86.4, 123.3$ (q, $J = 270.2$ Hz), 123.7 (q, $J = 4.4$ Hz), 125.8 (q, $J = 34.4$ Hz), 129.5, 142.6, 145.7 (q, $J = 2.9$ Hz); HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{18}\text{F}_3\text{O}$, $[\text{M}+\text{H}]^+ 259.1299$. Found m/z 259.1304.

1l:

Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 20/1); Yield 35%; IR (neat): 2930, 1601, 1452, 1265, 1080, 731 cm^{-1} ; ^1H NMR: $\delta = 0.89$ (t, $J = 7.2$ Hz, 3H), 1.22–1.40 (m, 3H), 1.44–1.59 (m, 1H), 1.80–1.91 (m, 1H), 2.00–2.09 (m, 1H), 3.06 (d, $J = 14.0$ Hz, 1H), 3.32 (d, $J = 14.4$ Hz, 1H), 3.35 (s, 3H), 5.13 (s, 2H), 6.74–6.80 (m, 2H), 7.22 (dd, $J = 8.4, 7.2$ Hz, 1H), 7.29–7.34 (m, 1H), 7.35–7.46 (m, 4H); ^{13}C NMR: $\delta = 14.9, 23.1, 27.2, 38.0, 39.5, 52.3, 70.3, 85.9, 112.4, 116.2, 127.2, 127.8, 128.5, 130.8, 132.8, 137.2, 143.5, 153.7$; HRMS (APCI): Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_2$, $[\text{M}+\text{H}]^+ 297.1849$. Found m/z 297.1843.

1m:

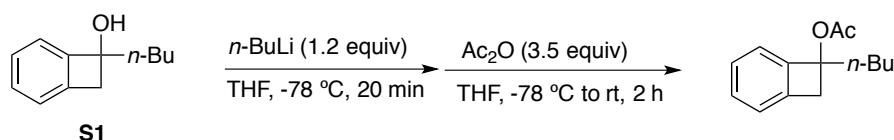
Purified by preparative thin-layer chromatography (hexane/ethyl acetate = 20/1); Yield 16%; IR (neat): 2928, 1456, 1080, 750, 696 cm^{-1} ; ^1H NMR: $\delta = 3.30$ (s, 3H), 3.40 (d, $J = 14.4$ Hz, 1H), 3.63 (d, $J = 14.0$ Hz, 1H), 7.19–7.37 (m, 7H), 7.37–7.44 (m, 2H); ^{13}C NMR: $\delta = 45.8, 53.2, 86.9, 123.1, 124.2, 126.7, 127.1, 127.5, 128.2, 129.6, 141.6, 142.4, 145.8$; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{15}\text{O}$, $[\text{M}+\text{H}]^+ 211.1117$. Found m/z 211.1112.

1n:

Purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1); Yield 17%; IR (neat): 2966, 1456, 1086, 739 cm^{-1} ; ^1H NMR: $\delta = 1.10$ (t, $J = 7.6$ Hz, 3H), 1.32 (d, $J = 7.2$ Hz, 3H), 1.66 (dq, $J = 14.8, 7.6$ Hz), 1.91 (dq, $J = 14.8, 7.6$ Hz), 3.28 (s, 3H),

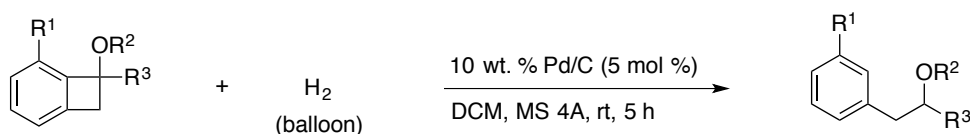
3.66 (q, $J = 7.2$ Hz, 1H), 7.11–7.18 (m, 1H), 7.28–7.23 (m, 2H), 7.26–7.32 (m, 1H); ^{13}C NMR: $\delta = 8.3, 13.9, 25.5, 46.6, 51.9, 87.3, 122.3, 122.5, 126.9, 129.1, 146.7, 146.8$; HRMS (APCI): Calcd for $\text{C}_{12}\text{H}_{17}\text{O}$, $[\text{M}+\text{H}]^+$ 177.1274. Found m/z 177.1269; The stereochemistry was determined by the analysis of NOE.

Synthesis of Acetoxycyclobutene **1c**

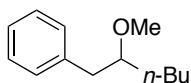


To a stirred solution of benzocyclobutenol **S1** (126 mg, 0.72 mmol) in THF (3.0 mL) was added $n\text{-BuLi}$ (hexane solution, 1.6 M, 0.54 mL, 0.87 mmol) slowly at $-78\text{ }^{\circ}\text{C}$. After stirring for 20 min at $-78\text{ }^{\circ}\text{C}$, Ac_2O (250 mg, 2.5 mmol) in THF (2.0 mL) was added dropwise to a reaction mixture. The obtained solution was stirred at rt for 2 h and then saturated NH_4Cl aq was added. The mixture was extracted with Et_2O , washed with water and brine, dried over MgSO_4 , and evaporated. After purification by chromatography on silica gel (hexane/ethyl acetate = 20/1), the desired product **1c** was obtained in 29% yield; IR (neat): 2957, 1734, 1236, 1020, 714 cm^{-1} ; ^1H NMR: $\delta = 0.89$ (t, $J = 6.8$ Hz, 3H), 1.24–1.46 (m, 4H), 2.02–2.14 (m, 1H), 2.05 (s, 3H), 2.20–2.32 (m, 1H), 3.36 (d, $J = 14.0$ Hz, 1H), 3.42 (d, $J = 14.4$ Hz, 1H), 7.15 (d, $J = 7.2$ Hz, 1H), 7.20–7.26 (m, 1H), 7.27–7.33 (m, 1H), 7.35 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR: $\delta = 14.0, 21.6, 22.8, 26.8, 34.9, 43.5, 85.9, 123.4, 123.8, 127.1, 129.6, 141.7, 146.9, 170.4$; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$, $[\text{M}+\text{H}]^+$ 219.1380. Found m/z 219.1376.

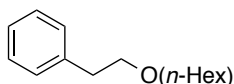
General procedure for a Pd/C-catalyzed reaction of alkoxybenzocyclobutenes



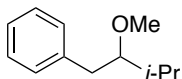
To the schlenk equipped with a stirrer bar were added 10 wt. % dried Pd/C (10.6 mg, 0.010 mmol, 5 mol % Pd) and MS 4A (20.0 mg) under argon atmosphere. The alkoxybenzocyclobutene (0.20 mmol) in DCM (3.0 mL) was added to the flask. After the argon gas was replaced with hydrogen gas, the solution was stirred at room temperature. The reaction mixture was filtered through a celite pad and concentrated. The residue was purified by preparative thin-layer chromatography or gel permeation chromatography to yield the ring-opening product.

2a:

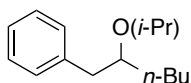
Purified by gel permeation chromatography; IR (neat): 2932, 1454, 1094, 698 cm^{-1} ; ^1H NMR: δ = 0.88 (t, J = 7.6 Hz, 3H), 1.23–1.50 (m, 6H), 2.70 (dd, J = 13.6, 6.4 Hz, 1H), 2.84 (dd, J = 13.6, 6.0 Hz, 1H), 3.32 (s, 3H), 3.30–3.40 (m, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR: δ = 14.1, 22.8, 27.5, 33.2, 40.1, 57.0, 82.4, 126.0, 128.2, 129.4, 139.2; HRMS (APCI): Calcd for $\text{C}_{13}\text{H}_{20}\text{ONa}$, $[\text{M}+\text{Na}]^+$ 215.1406. Found m/z 215.1406.

2e:

Purified by gel permeation chromatography; IR (neat): 2856, 1454, 1109, 696 cm^{-1} ; ^1H NMR: δ = 0.88 (t, J = 7.2 Hz, 3H), 1.50–1.60 (m, 2H), 2.88 (t, J = 7.6 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 3.32 (s, 3H), 3.61 (t, J = 7.2 Hz, 2H), 7.16–7.31 (m, 5H); ^{13}C NMR: δ = 14.0, 22.6, 25.8, 29.7, 31.7, 36.4, 71.1, 71.8, 126.1, 128.3, 128.9, 139.1; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{23}\text{O}$, $[\text{M}+\text{H}]^+$ 207.1743. Found m/z 207.1743.

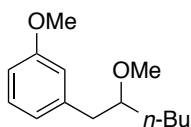
2g:

Purified by gel permeation chromatography; IR (neat): 2959, 1454, 1092, 698 cm^{-1} ; ^1H NMR: δ = 0.96 (d, J = 5.6 Hz, 3H), 0.97 (d, J = 6.0 Hz, 3H), 1.74–1.88 (m, 1H), 2.72 (dd, J = 13.6, 7.2 Hz, 1H), 2.76 (dd, J = 14.0, 5.2 Hz, 1H), 3.12–3.18 (m, 1H), 3.25 (s, 3H), 7.18–7.32 (m, 5H); ^{13}C NMR: δ = 17.6, 18.5, 30.7, 37.2, 58.3, 87.7, 125.8, 128.2, 129.3, 139.9; HRMS (APCI): Calcd for $\text{C}_{12}\text{H}_{18}\text{ONa}$, $[\text{M}+\text{Na}]^+$ 201.1250. Found m/z 201.1247.

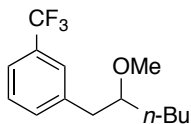
2h:

This product was obtained with a pure form after a filtration; IR (neat): 2932, 1454, 1038, 698 cm^{-1} ; ^1H NMR: δ = 0.93 (t, J = 7.6 Hz, 3H), 1.05 (d, J = 6.0 Hz, 3H), 1.16 (d,

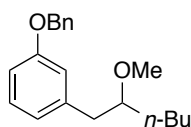
$J = 6.0$ Hz, 3H), 1.26–1.39 (m, 3H), 1.41–1.54 (m, 3H), 2.74 (dd, $J = 13.6, 6.0$ Hz, 1H), 2.82 (dd, $J = 13.6, 6.4$ Hz, 1H), 3.46–3.60 (m, 2H), 7.21–7.27 (m, 3H), 7.30–7.35 (m, 2H); ^{13}C NMR: $\delta = 14.9, 22.5, 22.8, 27.9, 34.7, 41.9, 70.1, 78.5, 125.9, 128.1, 129.6, 139.5$; HRMS (APCI): Calcd for $\text{C}_{15}\text{H}_{24}\text{ONa}$, $[\text{M}+\text{Na}]^+ 243.1719$. Found m/z 243.1715.

2j:

Purified by gel permeation chromatography; IR (neat): 2932, 1601, 1489, 1259, 1094, 696 cm^{-1} ; ^1H NMR: $\delta = 0.84\text{--}0.92$ (m, 3H), 1.22–1.50 (m, 6H), 2.67 (dd, $J = 14.0, 6.4$ Hz, 1H), 2.82 (dd, $J = 13.6, 6.0$ Hz, 1H), 3.32 (s, 3H), 3.33–3.40 (m, 1H), 3.80 (s, 3H), 6.73–6.78 (m, 2H), 6.80 (d, $J = 7.6$ Hz, 1H), 7.20 (dd, $J = 7.6, 7.6$ Hz, 1H); ^{13}C NMR: $\delta = 14.1, 22.8, 27.5, 33.3, 40.2, 55.1, 57.0, 82.3, 111.2, 115.2, 121.8, 129.1, 140.9, 159.5$; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2\text{Na}$, $[\text{M}+\text{Na}]^+ 245.1512$. Found m/z 245.1508.

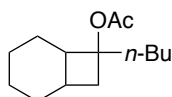
2k:

Purified by gel permeation chromatography; IR (neat): 2932, 1327, 1123, 1072, 702 cm^{-1} ; ^1H NMR: $\delta = 0.86\text{--}0.94$ (m, 3H), 1.24–1.54 (m, 6H), 2.78 (dd, $J = 13.6, 5.2$ Hz, 1H), 2.85 (dd, $J = 14.0, 6.8$ Hz, 1H), 3.30 (s, 3H), 3.31–3.40 (m, 1H), 7.36–7.43 (m, 2H), 7.44–7.49 (m, 2H); ^{13}C NMR: $\delta = 14.0, 22.8, 27.4, 33.2, 40.0, 57.1, 81.9, 122.9$ (q, $J = 3.7$ Hz), 126.0 (q, $J = 4.4$ Hz), 128.5, 130.5 (q, $J = 31.5$ Hz), 132.8, 140.2; HRMS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{OF}_3$, $[\text{M}-\text{H}]^+ 259.1310$. Found m/z 259.1307.

2l:

Purified by gel permeation chromatography; IR (neat): 2928, 1582, 1258, 1094, 694 cm^{-1} ; ^1H NMR: $\delta = 0.88$ (t, $J = 7.2$ Hz, 3H), 1.22–1.50 (m, 6H), 2.66 (dd, $J = 13.6, 6.4$ Hz, 1H), 2.82 (dd, $J = 13.6, 6.4$ Hz, 1H), 3.31 (s, 3H), 3.34 (dddd, $J = 12.0, 12.0, 6.0$,

6.0, 1H), 5.06 (s, 2H), 6.79–6.86 (m, 2H), 6.85 (s, 1H), 7.20 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.30–7.36 (m, 1H), 7.39 (dd, $J = 7.2$, 7.2 Hz, 2H), 7.44 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR: $\delta = 14.1$, 22.8, 27.5, 33.3, 40.2, 57.0, 69.9, 82.3, 112.2, 116.1, 122.1, 127.5, 127.9, 128.5, 129.2, 137.1, 140.9, 158.7.

3c:

Purified by gel permeation chromatography; IR (neat): 2928, 1732, 1254, 1016 cm^{-1} ; ^1H NMR: $\delta = 0.88$ (t, $J = 7.2$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H*), 1.08–1.36 (m, 7H + 7H*), 1.41–1.54 (m, 2H + 2H*), 1.57–1.89 (m, 5H + 5H*), 1.98 (s, 3H*), 1.99 (s, 3H), 2.08–2.17 (m, 1H + 1H*), 2.21–2.29 (m, 1H + 1H*), 2.32–3.42 (m, 1H + 1H*), 2.48–2.56 (m, 1H + 1H*); ^{13}C NMR: $\delta = 14.1$, 14.1*, 21.4*, 21.6*, 21.9, 22.0*, 22.1, 22.2, 22.3, 22.6*, 22.9*, 22.9, 25.4, 25.69*, 25.73*, 26.1*, 26.1, 27.6, 33.1*, 34.7*, 34.9*, 36.8, 42.0, 42.6*, 81.0*, 87.0, 169.9*, 170.2; HRMS (APCI): Calcd for $\text{C}_{14}\text{H}_{25}\text{O}_2\text{Na}$, $[\text{M}+\text{H}]^+$ 225.1849. Found m/z 225.1845.

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8. Over reduction of benzene ring was observed, see: Blazejewski, J.-C.; Haddad, M.; Wakselman, C. *Tetrahedron Lett.* **1994**, 35, 2021.
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List of Publications

Chapter 1

Synthesis of 3,3-disubstituted α -tetralones by rhodium-catalysed reaction of 1-(2-haloaryl)cyclobutanols

Naoki Ishida, Shota Sawano, Masahiro Murakami

Chem. Commun. **2012**, 48, 1973-1975.

Chapter 2

Rhodium-Catalyzed Ring Opening of Benzocyclobutenols with Site-Selectivity Complementary to Thermal Ring Opening

Naoki Ishida, Shota Sawano, Yusuke Masuda, Masahiro Murakami

J. Am. Chem. Soc. **2012**, 134, 17502-17504.

Chapter 3

Construction of tetralin skeletons based on rhodium-catalysed site-selective ring opening of benzocyclobutenols

Naoki Ishida, Norikazu Ishikawa, Shota Sawano, Yusuke Masuda, Masahiro Murakami

Chem. Commun. **2015**, 51, 1882-1885.

Chapter 4

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

Naoki Ishida, Shota Sawano, Masahiro Murakami

Nature Commun. **2014**, 5, 3111.

Chapter 5

Ring Opening of Alkoxybenzocyclobutenes with Site-Selective Hydrogenolysis of C(sp²)-C(sp³) Bond

Shota Sawano, Naoki Ishida, Masahiro Murakami

To be submitted