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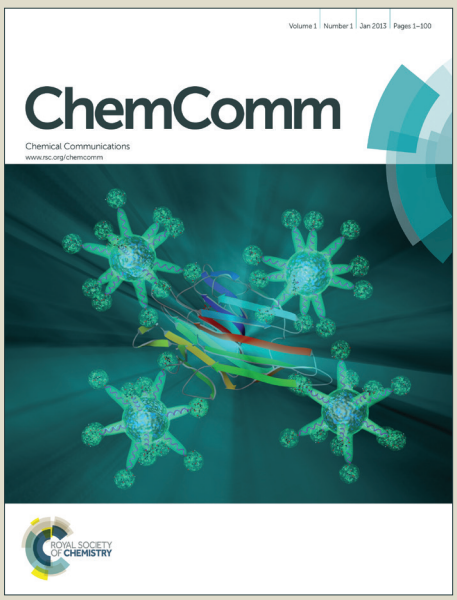

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Construction of tetralin skeletons based on rhodium-catalysed site-selective ring opening of benzocyclobutenols

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

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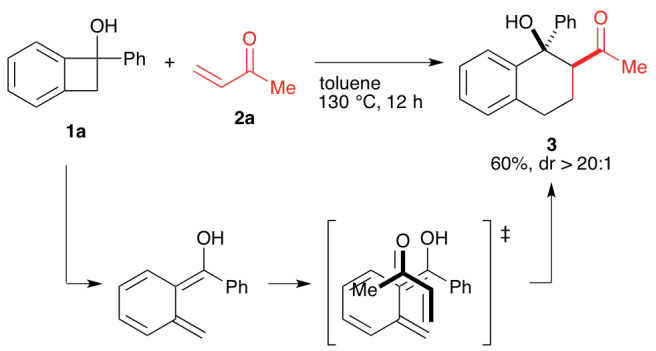
Tetralins (tetrahydronaphthalenes) are synthesised from benzocyclobutenols based on the rhodium-catalysed site-selective ring opening followed by intermolecular/intramolecular conjugate addition of the resulting arylrhodium species to electron-deficient alkenes. The produced structures make a remarkable contrast with those available from the same compounds under thermal reaction conditions.

Tetralin is a key structural motif found in a wide variety of bioactive molecules including natural products such as heritonine,[1] cycloolivil,[2] morphine[3] and daunorubicin.[4] The development of efficient methods for the construction of tetralin skeleton has been a subject of intense research. We report herein a new protocol to prepare tetralin derivatives from benzocyclobutenols based on their site-selective ring opening under the catalysis of rhodium.[5-8] 2-Hydroxytetralins are stereoselectively synthesised by an insertion reaction of vinyl ketones into the C(sp^2)–C(sp^3) bond of benzocyclobutenols. The rhodium-catalysed rearrangement of 1-alkenylbenzocyclobutenols furnishes 2-tetralones. The produced structures make a remarkable contrast with those available from the same compounds under thermal reaction conditions.

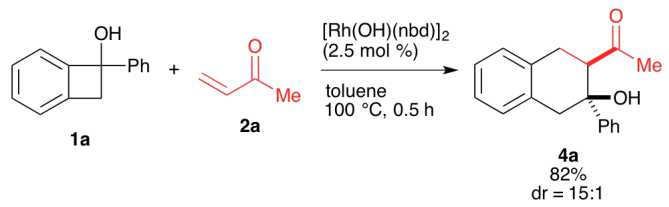
A [4+2] cycloaddition reaction of *o*-quinodimethanes with alkenes presents one of the most reliable synthetic pathways to tetralin skeletons.[9] For example, when benzocyclobutenols are heated, a thermal ring opening reaction takes place with outward rotation of the hydroxyl group[10] to stereoselectively furnish the hydroxy-substituted *o*-quinodimethanes. A regioselective [4+2] cycloaddition reaction with electron-deficient alkenes follows in an *endo* fashion.[11] Thus, simple heating of a toluene solution of benzocyclobutenol **1a** and methyl vinyl ketone (**2a**) at the refluxing temperature (bath temperature: 130 °C) gave 1-hydroxytetralin **3** in a diastereoselective fashion (Scheme 1). It has been also known that treatment of benzocyclobutenols with butyllithium generates an oxyanion intermediate, which follows an analogous pathway even at −78 °C.[12] In these cases, the C–C double bond is formally inserted into the C(sp^3)–C(sp^3) bond of the cyclobutene ring.



Scheme 1 Thermal reaction of **1a** and **2a**.

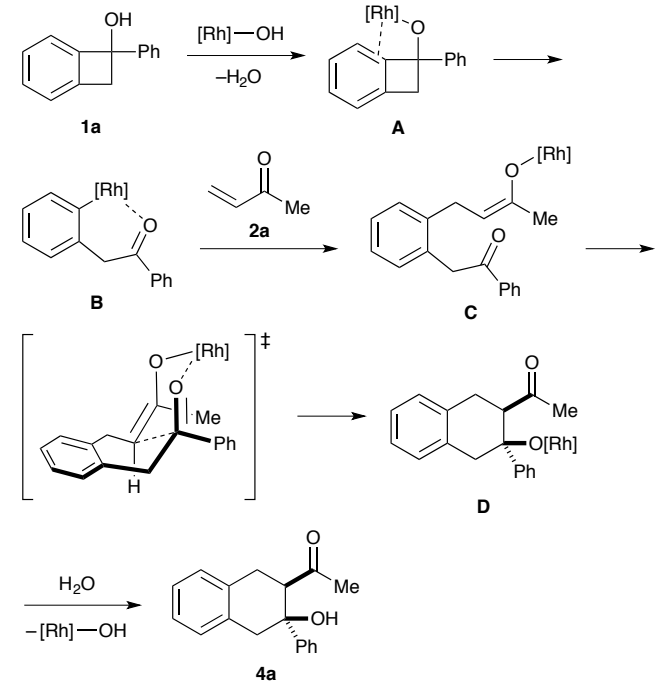
On the other hand, we have reported a different type of ring opening reaction of benzocyclobutenols; a rhodium complex prompts ring opening selectively at the C(sp^2)–C(sp^3) bond to furnish an *ortho*-acylmethyl-substituted arylrhodium intermediate.[5,13,14] The subsequent intermolecular addition across the C–C triple bond of alkynes generates alkenylrhodium species, which then undergoes intramolecular addition onto the carbonyl group to construct dihydronaphthalene frameworks. In a formal sense, a C–C triple bond is inserted into the C(sp^2)–C(sp^3) bond of the cyclobutene ring in an atom-economical way. This finding led us to explore new synthetic pathways leading to tetralins (tetrahydronaphthalenes) from benzocyclobutenol derivatives.

We first carried out a thermal reaction of **1a** and **2a** at 100 °C for 30 min in the absence of a rhodium catalyst. The thermal ring-opening reaction of **1a** was so slow that 90% of **1a** was recovered. Next, **1a** was reacted with **2a** in the presence of [Rh(OH)(nbd)]$_2$ under otherwise identical conditions. The C–C double bond of **2a** was successfully inserted into the C(sp^2)–C(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 2. Rhodium-catalysed reaction of **1** and **2**.

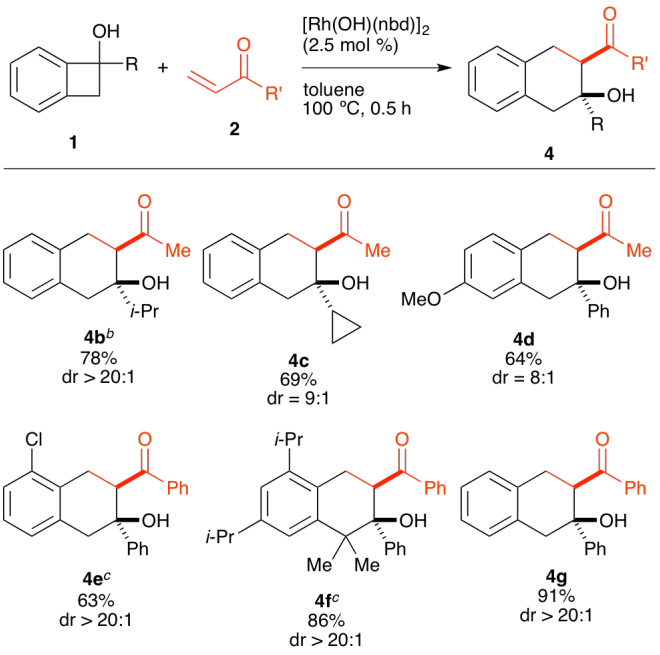
A probable mechanistic scenario for the diastereoselective formation of **4a** is depicted in Scheme 3. Initially, the hydroxylic proton of benzocyclobutenol **1a** is exchanged with rhodium to furnish the rhodium benzocyclobutenolate **A**. The benzene ring π-coordinates to the rhodium centre,[15] and the π-coordination is retained during the subsequent β-carbon elimination so that the ipso carbon selectively migrates on rhodium. Thus, the C(sp^2)–C(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 follows again via a six-membered transition state, for which chair-like conformation is assumed to afford *syn*-aldolate **D** stereoselectively.[16,17] Protonation of **D** with water, generated in the first step, or with **1a** produces **4a** and the next catalytic cycle starts over.



Scheme 3. 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 sp^2 carbon was obstructed by its *ortho*-isopropyl group. Phenyl vinyl ketone also successfully engaged in the insertion reaction. On the other hand, alkenes lacking electron-withdrawing groups (e.g. ethylene and styrene) failed to be incorporated. 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).

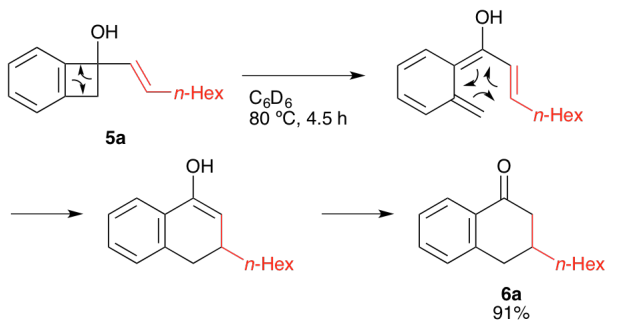
Table 1 Rhodium-catalysed reactions of **1** and **2**. [a]



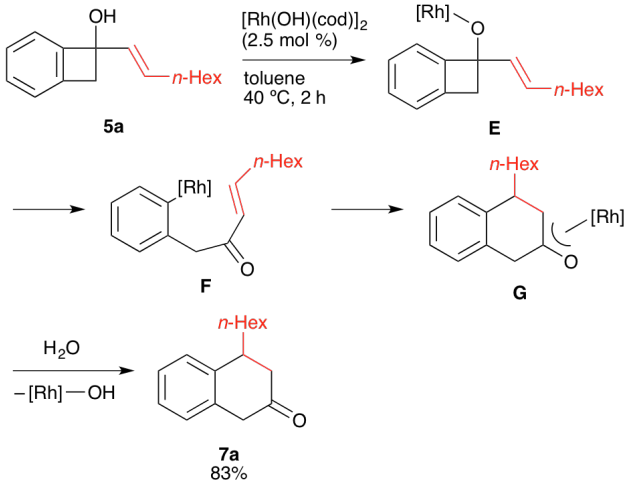
[a] Reaction conditions: Benzocyclobutenol **1** (0.20 mmol), vinyl ketone **2** (0.40 mmol, 2 equiv), $[Rh(OH)(nbd)]_2$ (2.5 mol %), toluene (1 mL), 100 °C, 0.5 h. Isolated yields of the major diastereomer were shown. Dr were determined by NMR analysis of the crude reaction mixture. [b] 1 h. [c] $[Rh(OH)(cod)]_2$ (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 with analogous substrates (Scheme 4).[18] 4π-Ring opening of **5a** is followed by 6π-electrocyclic ring closure to afford **6a**. In sharp contrast, treatment of **5a** with a catalytic amount of $[Rh(OH)(cod)]_2$ at 40 °C for 2 h gave 2-tetralone **7a** in 83% isolated yield.[19] Mechanistically, it is assumed the site-selective cleavage of the C(sp^2)–C(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 follows, and the resulting oxa-π-allylrhodium **G** is protonated with water, or with **5a** to give **7a**.

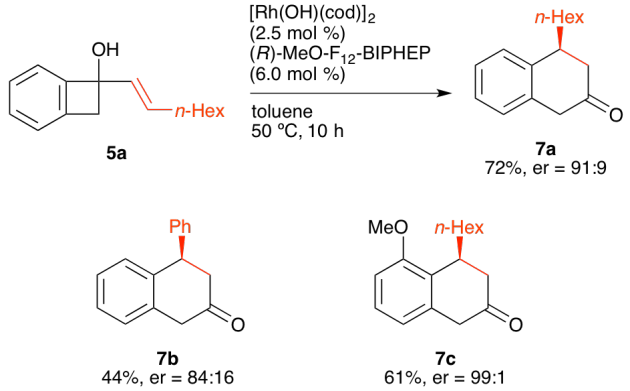
Thus, the pathway of the intramolecular rearrangement reaction of **5a** is also changed by a rhodium complex. In addition, the racemic mixture of **5a** was enantioselectively rearranged when electron-deficient chiral diphosphine (*R*)-MeO-F_{12}-BIPHEP[20] was employed as the ligand for rhodium. 2-Tetralone **7a** was obtained in 72% yield with the enantiomeric ratio (er) of 91:9. The reaction conditions were applied to the synthesis of **7b** (er = 84:16) and **7c** (er = 99:1).



Scheme 4. Thermal rearrangement of **5a**.



Scheme 5. Rhodium-catalysed rearrangement of **5a**.



Scheme 6. Asymmetric rearrangement of **5**.

In summary, tetralin skeletons are constructed from benzocyclobutenols based on the rhodium-catalysed site-selective ring opening reaction. Vinyl ketones are site-selectively inserted into the $C(sp^2)$–$C(sp^3)$ bond of benzocyclobutenols to produce 2-hydroxytetralins. 1-Alkenylbenzocyclobutenols are restructured into 2-tetralones. The obtained tetralins markedly contrast with those given by the conventional thermal reactions.

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Notes and references

Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510, Japan. E-mail: murakami@sbchem.kyoto-u.ac.jp; Fax: (+81)-75-383-2748; Tel: (+81)-75-383-2747.

† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, and spectral data for all compounds, including scanned images of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c000000x/.

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