Rhodium(I)-Catalyzed Enantioselective Cyclization of Enynes via Intramolecular Cleavage of the Rh-C Bond by a Tethered Hydroxy Group

Yoshihiro Oonishi,* Shuichi Masusaki, Shunki Sakamoto, and Yoshihiro Sato*

Abstract: Rhodium(I)-catalyzed enantioselective intramolecular cyclization of enynes having a hydroxy group in the tether was investigated, and various cyclic compounds possessing a chiral quaternary carbon center were obtained in high yields with high ees. In this cyclization, an Rh-C(sp^2) bond in the rhodacyclopentene intermediate, which was formed via enantioselective oxidative cycloaddition of enynes to a chiral rhodium(I) complex, was intramolecularly cleaved by σ-bond metathesis of a tethered O-H bond in the substrate. Furthermore, it was found that the cyclic compounds were obtained with high ees even when the starting materials having a racemic secondary alcohol moiety were used in this reaction.

Transition metal-catalyzed enantioselective cyclization of enynes bearing a 1,1-disubstituted alkene has emerged as an attractive strategy for efficient construction of various carbo- and heterocyclic compounds possessing a chiral quaternary carbon center (Scheme 1).[1] It is well known that these reactions proceed through metallacyclopentene **A**, which is formed by enantioselective oxidative cycloaddition of alkyne and alkene of enynes to a chiral transition metal complex (M-L_n^*). Although *intermolecular* cyclization between a metallacyclopentene intermediate and other reactants (e.g., Pauson-Khand reaction, [2 + 2 + 2] cycloaddition, *etc*.) has been investigated in detail,[2] *intramolecular* variants remain rare.[3-5] Shibata and coworker reported rhodium(I)-catalyzed intramolecular cyclization of enyne, having an additional alkene in the tether (eq. 1).[3a,3b] Tanaka and coworkers also reported two types of enantioselective intramolecular cyclizations: one is rhodium(I)-catalyzed [2 + 2 + 2] cycloaddition of enynes with a tethered carbonyl group[4] and the other is rhodium(I)-catalyzed cyclization of enynes through sp^3 C-H bond activation.[5] We herein report rhodium(I)-catalyzed enantioselective *intramolecular* cyclization of enyne,[6] having a hydroxy group in the tether, to afford a cyclic compound possessing a chiral quaternary carbon center (eq. 2).

Initially, the cyclization of substrate **1a** using various rhodium(I) complexes was examined (Table 1). The use of achiral bindentate phosphines such as dppe and dppp did not afford the cyclic compound **2a**, and the starting material **1a** was recovered (entries 1 and 2). The cyclization of **1a** with Rh^+/BIPHEP proceeded smoothly, giving the cyclic compound **2a** in good yield (entry 3).[7] Encouraged by this result, we further investigated the use of various chiral ligands in this cyclization, with focus on BINAP-type ligands having a biaryl structure like BIPHEP (entries 4-7). Among the ligands, (*R*)-H_8-BINAP was the most effective ligand in this cyclization, giving **2a** in 79% yield with 86% ee (entry 7). It was also found that the cyclization proceeded even at 40 °C without greatly decreasing the yield and the ee by using (*R*)-H_8-BINAP as a ligand (entry 8). Next, the influence of a counter anion on this reaction was examined (entries 9-11). It was found that the use of BAr^F anion shortened the reaction time and improved the enantioselectivity, giving **2a** in 73% yield and 94% ee (entry 11).[8]

Scheme 1. Transition metal-catalyzed enantioselective cyclization of enyne, having a 1,1-disubstituted alkene.

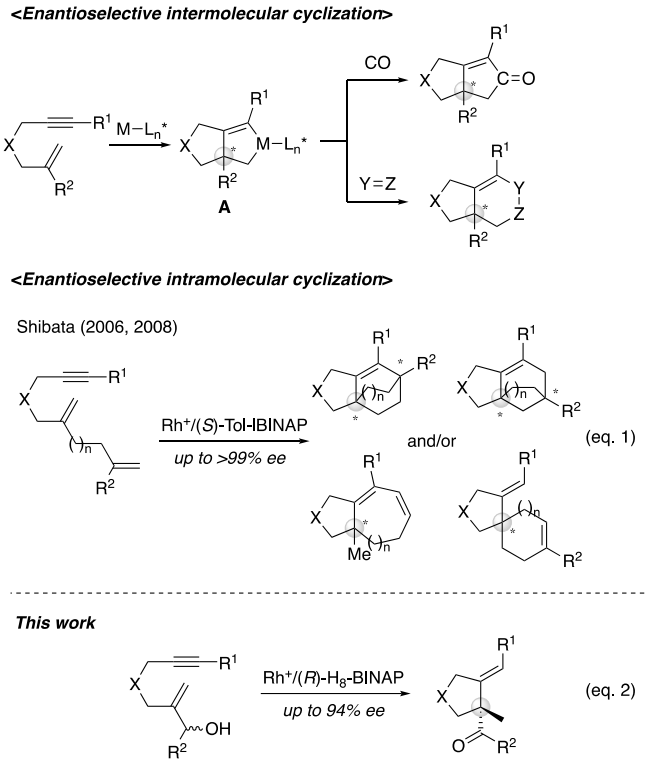
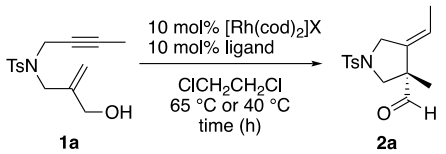


Table 1. Cyclization of enyne **1a** under various conditions.[a]



Entry	Ligand	Anion (X)	Time (h)	Yield (%)	Ee (%)
1[b]	dppe	BF_4	14	-	-
2[b]	dppp	BF_4	22	-	-
3	BIPHEP	BF_4	3	70	-
4	(*R*)-BINAP	BF_4	21	78	85
5	(*R*)-Tol-BINAP	BF_4	3	70	85
6	(*R*)-Xyl-BINAP	BF_4	20	76	84
7	(*R*)-H_8-BINAP	BF_4	4	79	86

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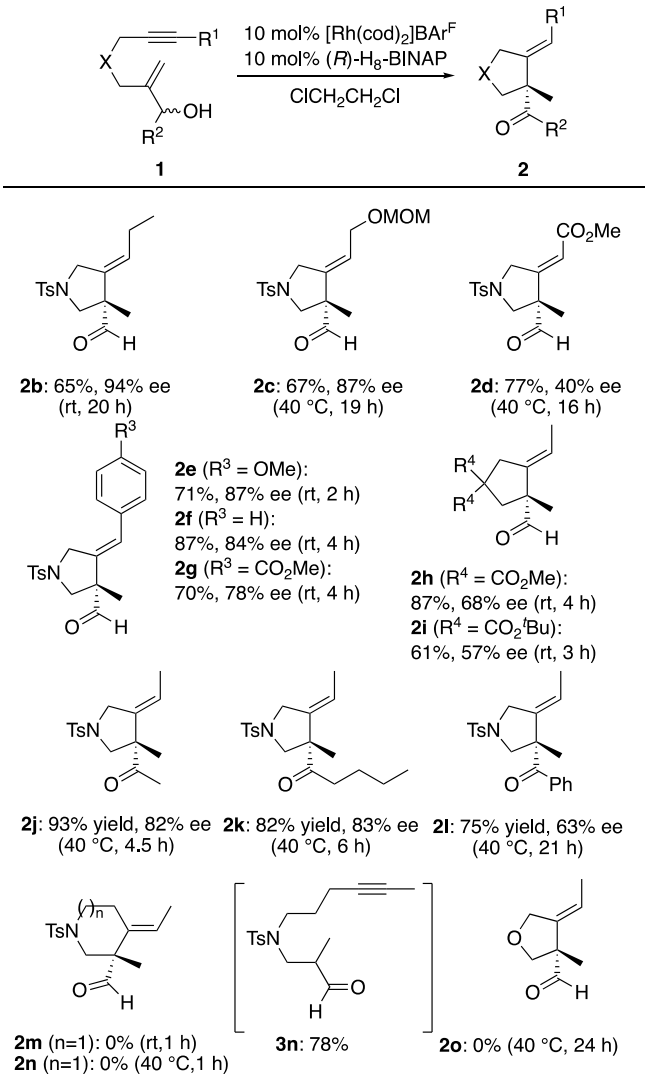
8	(*R*)-H_8-BINAP	BF_4	20	78	89
9	(*R*)-H_8-BINAP	ClO_4	24	63	85
10	(*R*)-H_8-BINAP	SbF_6	18	71	92
11	(*R*)-H_8-BINAP	BAr^F	7	73	94

[a] $[Rh(cod)_2]X$ (0.016 mmol), ligand (0.016 mmol), **1a** (0.016 mmol), and $ClCH_2CH_2Cl$ (1.6 mL) were employed. The reaction was carried out at 65 °C (entries 1-7) and at 40 °C (entries 8-11). [b] **1a** was recovered in 100% yield (entry 1) and in 90% yield (entry 2).

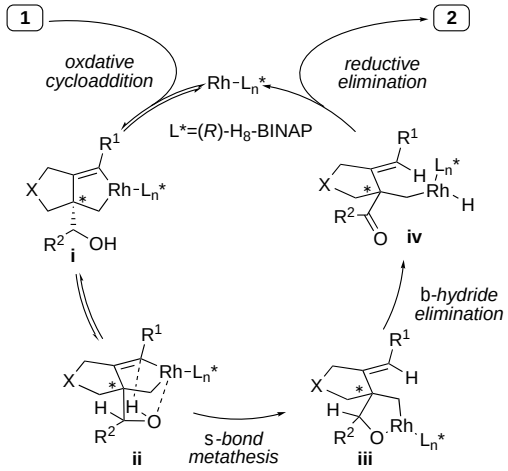
With the optimal conditions in hand, the scope and limitations of this cyclization were tested (Table 2). The cyclization of **1b** and **1c**, having an ethyl or MOM group on the alkyne moiety, proceeded smoothly, giving the desired cyclic compounds **2b** and **2c** in good yields with high ees. When **1d**, having an electron-withdrawing group on the alkyne moiety, was employed in this reaction, **2d** was obtained in 77% yield, albeit with low ee. The cyclization of **1e**-**1g**, bearing an aromatic ring on the alkyne moiety, afforded the cyclic compounds **2e**-**2g** in good yields with good ees.[9] This cyclization is applicable for the construction of a carbocyclic ring, in which case, however, the ees of products **2h** and **2i** are moderate.[9,10] Interestingly, the reactions of substrates **1j**-**1l**, having a racemic secondary alcohol moiety, also proceeded, giving the corresponding cyclic compounds **2j**-**2l** in high yields with moderate to high ees. On the other hand, the cyclization of 1,7 - enyne **1m** did not afford the desired product **2m**, but the complex mixtures (an unidentified product as a major product along with various by - products) were produced. In the reaction of 1,8 - enyne **1n**, the aldehyde **3n** was obtained in 78 % yield through isomerization of allylic alcohol moiety, probably owing to the difficulty of formation of the seven - membered ring of **2n**. When the cyclization of **1o**, having an oxygen atom in the tether, was carried out, the desired product **2o** was not obtained, resulting in complex mixtures.

Table 2. Rhodium(I)-catalyzed cyclization of various enynes **1**.



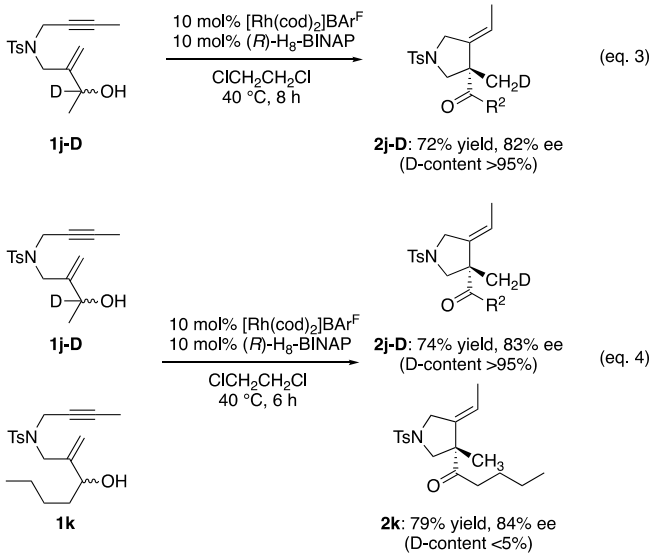
A possible mechanism of this cyclization is depicted in Scheme 2. Initially, enantioselective oxidative cyclization of alkyne and alkene of the substrate **1** to the chiral Rh^+/(*R*)-H_8-BINAP complex occurs to form the rhodacycle intermediate **i**, which would contain a chiral carbons center at the ring-junction.[11] Coordination of an oxygen atom of the hydroxy group to the cationic rhodium(III) center (i.e., the intermediate **ii**) would trigger cleavage of the Rh-C(sp^2) bond via σ-bond metathesis between the Rh-C(sp^2) bond and O-H, giving rhodacycle intermediate **iii**. Subsequently, β-hydride elimination from **iii** followed by reductive elimination from **iv** takes place to afford the cyclic compound **2** having a chiral quaternary carbon center.

Scheme 2. Possible reaction mechanism for the formation of **2**.



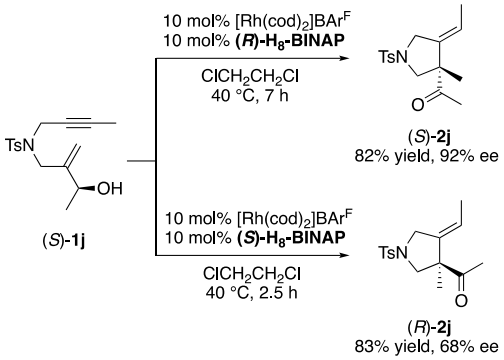
In order to gain mechanistic insights, additional experiments were performed (Scheme 3). First, the deuterated substrate **1j-D** was subjected to the above-mentioned optimal reaction conditions. As a result, the corresponding product **2j-D**, having a deuterium at the methyl group, was produced in high yield and high ee with a high D-content (eq. 3), being consistent with the mechanism (especially at the stage from intermediate **iii** to **iv**) shown in Scheme 2. Second, a crossover experiment using **1j-D** and **1k** was carried out, and **2j-D** with a high D-content and **2k** without incorporation of deuterium were obtained in reasonable yields and ees. These results indicate that the sequence reactions in the catalytic cycle (i.e., cleavage of the Rh-C(sp^2) bond via σ-bond metathesis to form intermediate **iii** from **ii**, β-hydride elimination from **iii,** and reductive elimination from **iv**) proceed entirely in an intramolecular process (eq. 4).[12]

Scheme 3. Mechanistic studies.



As mentioned above, the products **2j**-**2l** were produced in high ee even though the *racemic* starting materials **1j**-**1l** were used in this cyclization (Table 1). Thus, we checked the effect of the absolute configuration of substrates **1j**-**1l** on the reactivity and enantioselectivity of the cyclization (Scheme 4). When the reaction of optically pure (>99% ee) (*S*)-**1j** using (*R*)-H_8-BINAP was carried out, the product (*S*)-**2j** was obtained in 82% yield with 92% ee, results that are the comparable to results of the reaction of racemic **1j** shown in Table 2. On the other hand, the cyclization of (*S*)-**1j** using (*S*)-H_8-BINAP afforded the cyclic compound (*R*)-**2j** in 83% yield with 68% ee. These results suggest that the absolute configuration of the product **2j** is basically controlled by the chirality of the ligand. Furthermore, the decrease of the product's ee when the combination of an (*S*)-substrate and an (*S*)-ligand was used also suggests that this combination and vice versa (i.e., the combination of an (*R*)-substrate and an (*R*)-ligand) would be a mismatched pair, while the combination of an (*S*)-substrate and an (*R*)-ligand (or an (*R*)-substrate and an (*S*)-ligand) would be a matched pair in the cyclization.

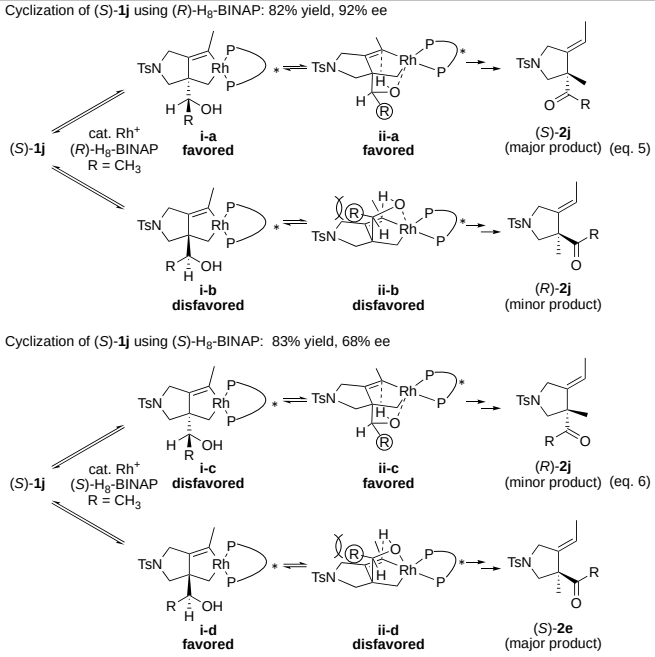
Scheme 4. Cyclization of (*S*)-**1j** with Rh^+/(*R*)- or (*S*)-H_8-BINAP.



The different enantioselectivities in these cyclizations of a chiral substrate can be explained as follows (Scheme 5). In the cyclization of (*S*)-**1j** using (*R*)-H_8-BINAP (which is considered as a matched pair), the rhodacycle **i-a** would be formed in preference to the rhodacycle **i-b** (eq. 5).[11] Subsequently, σ-bond metathesis between the Rh-C(sp^2) bond and O-H bond in the rhodacycle **ii-a** seems to occur without any interference to form the product (*S*)-**2j**. On the other hand, σ-bond metathesis in the rhodacycle **ii-b** would be retarded due to the steric repulsion between the substituent (R) and the pyrrolidine structure of **ii-b**, resulting in the product (*S*)-**2j** instead of (*R*)-**2j** being obtained through equilibration of rhodacycles **i-a**, **i-b**, **ii-a**, and **ii-b**.[13] On the other hand, in the cyclization of (*S*)-**1j** using (*S*)-H_8-BINAP (i.e., a mismatched pair), the formation of the rhodacycle **i-d** should be preferred to that of the rhodacycle **i-c** (eq. 6). However, the steric repulsion between the substituent (R) and the rhodacycle in **ii-d** would somewhat retard to form (*S*)-**2e**. As a result, in this case, the reaction would proceed through not only **ii-d** but also **ii-c**, resulting in a decrease in ee of the product.

In conclusion, we have developed a novel rhodium(I)-catalyzed enantioselective intramolecular cyclization of enyne, having a hydroxy group in the tether, that affords various cyclic compounds with a chiral quaternary carbon center in high yields with high ees. The noteworthy point of this reaction is that the Rh-C(sp^2) bond in the rhodacyclopentene intermediate formed via enantioselective oxidative cycloaddition of enynes to a chiral rhodium(I) complex is intramolecularly cleaved by σ-bond metathesis of a tethered O-H bond in the substrate. It is also noteworthy that various cyclic compounds, having a ketone moiety, were successfully obtained from racemic starting materials with high ees. Further studies along these lines are currently in progress.

Scheme 5. Possible reaction course.



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Keywords: rhodium • cyclization • enyne • enantioselective • σ-bond metathesis

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[2] For selected examples of enantioselective Pauson-Khand reaction, see: a) K. Hiroi, T. Watanabe, R. Kawagishi, I. Abe, *Tetrahedron Lett.* **2000**, *41*, 891; b) K. Hiroi, T. Watanabe, R. Kawagishi, I. Abe, *Tetrahedron: Asymmetry*, **2000**, *11*, 797; For selected examples of enantioselective [2+2+2] cycloaddition, see: c) P. A. Evans, K. W. Lai, J. R. Sawyer, *J. Am. Chem. Soc.* **2005**, *127*, 12466; d) T. Shibata, Y. Arai, Y. Tahara, *Org. Lett.* **2005**, *7*, 4955; e) K. Masutomi, N. Sakiyama, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.* **2012**, *51*, 13031; *Angew. Chem.* **2012**, *124*, 13208; f) K. Masutomi, H. Sugiyama, H. Uekusa, Y. Shibata, K. Tanaka, *Angew. Chem. Int. Ed.* **2016**, *55*, 15373; *Angew. Chem.* **2016**, *128*, 15599; g) H. Ueda, K. Masutomi, Y. Shibata, K. Tanaka, *Org. Lett.* **2017**, *19*, 2913; h) K. Tanaka, Y. Otake, H. Sagae, K. Noguchi, M. Hirano, *Angew. Chem. Int. Ed.* **2008**, *47*, 1312; *Angew. Chem.* **2008**, *120*, 1332; i) M. Ishida, Y. Shibata, K. Noguchi, K. Tanaka, *Chem. Eur. J.* **2011**, *17*, 12578.

[3] a) T. Shibata, Y. Tahara, *J. Am. Chem. Soc.* **2006**, *128*, 11766; b) T. Shibata, Y. Tahara, K. Tamura, K. Endo, *J. Am. Chem. Soc.* **2008**, *130,* 3451.

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[5] K. Masutomi, K. Noguchi, K. Tanaka, *J. Am. Chem. Soc.* **2014**, *136*, 7627.

[6] For our recent studies on rhodium(I)-catalyzed cyclization of enyne, see: a) Y. Oonishi, Y. Hato Y. Sato, *Adv. Synth. Catal.* **2016**, *358*, 2273; b) Y. Hato, Y. Oonishi, Y. Yamamoto, K. Nakajima, Y. Sato, *J. Org. Chem.* **2016**, *81*, 7847.

[7] The geometry of alkene in **2a** was determined by NOESY.

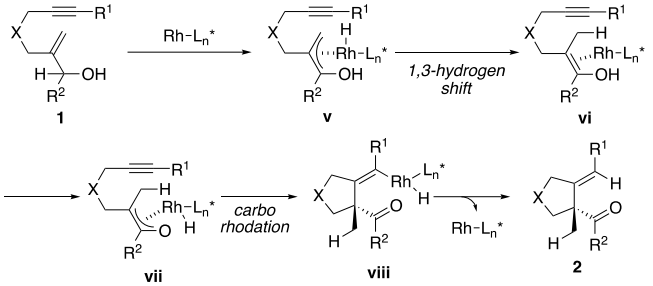
[8] When the reaction of **1a** was carried out using 2.5 mol% or 1 mol% [Rh((*R*)-H_8-binap)]BAr^F under the same conditions except for the catalyst loading, **2a** was obtained in 74% yield with 93% ee (24 h) or in 31% yield with 95% ee (90 h).

[9] The ee of **2g** and **2i** was determined after reduction of the aldehyde moiety.

[10] The absolute configuration of **2i** was assigned after chemical transformation (See Supporting Information for details.). The stereochemistry of cyclic compounds **2a-2l** was assigned by analogy to **2i**.

[11] Tanaka reported that the formation of rhodacycle intermediate having a chiral carbon center at the ring-junction occurred by enantioselective oxidative cycloaddition of enynes bearing a 1,1-disubstituted alkene to an Rh^+/(*R*)-H_8-BINAP complex in rhodium(I)-catalyzed enantioselective [2 + 2 + 2] cycloaddition. See ref. [2e].

[12] An alternative mechanism for the formation of **2** was also thought. Thus, the rhodium intermediate **v** was formed from **1**, then 1,3-hydrogen shift of **v** occurred to give **vi**. Subsequently, the oxa-π-allyl rhodium intermediate **vii** was formed from **vi**, which was followed by carborhodation of **vii** and reductive elimination from **viii** to give the same product **2.** At this stage, we cannot rule out either of the possibilities.



[13] It has been reported that the oxidative cycloaddition step of enyne with a rhodium complex is in equilibrium. See ref. [2e].

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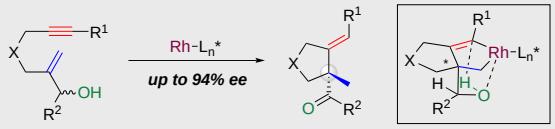

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