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 enantioselectivities. In this cyclization, an Rh-C(sp²) 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 enantiomeric excess 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-L₄⁺). 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 coworkers 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[5] and the other is rhodium(I)-catalyzed cyclization of enynes through sp²-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 bisphosphine 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 bidentate structure like BIPHEP (entries 4-7). Among the ligands, (R)-H₂-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 ºC without greatly decreasing the yield and the ee by using (R)-H₂-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 BAr₄ 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.

<Enantioselective intermolecular cyclization>

<Enantioselective intramolecular cyclization>

This work

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Anion (X)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td>dppe</td>
<td>BF₄</td>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2[a]</td>
<td>dppp</td>
<td>BF₄</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>BIPHEP</td>
<td>BF₄</td>
<td>3</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(R)-BINAP</td>
<td>BF₄</td>
<td>21</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>(R)-Tol-BINAP</td>
<td>BF₄</td>
<td>3</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>(R)-Xy-BINAP</td>
<td>BF₄</td>
<td>20</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>(R)-H₂-BINAP</td>
<td>BF₄</td>
<td>4</td>
<td>79</td>
<td>86</td>
</tr>
</tbody>
</table>

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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. This cyclization is applicable for the construction of a carbocyclic ring, in which case, however, the ees of products 2h and 2i are moderate. 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. 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)-H8-BINAP complex occurs to form the rhodacycle intermediate i, which would contain a chiral carbons center at the ring-junction. 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(sp2) bond via σ-bond metathesis between the Rh-C(sp2) 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(sp²) 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).

**Scheme 3.** Mechanistic studies.

As mentioned above, the products 2j-2l were produced in high ee even though the racemic starting materials 1j-11 were used in this cyclization (Table 1). Thus, we checked the effect of the absolute configuration of substrates 1j-11 on the reactivity and enantioselectivity of the cyclization (Scheme 4). When the reaction of optically pure (>99% ee) (S)-1j using (R)-H₂-BINAP was carried out, the product (S)-2j was obtained in 82% yield with 92% ee, results that are comparable to results of the reaction of racemic 1j shown in Table 2. On the other hand, the cyclization of (S)-1j using (S)-H₂-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)-H₂-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)-H₂-BINAP (which is considered as a matched pair), the rhodacycle i-a would be formed in preference to the rhodacycle i-b (eq. 5). Subsequently, σ-bond metathesis between the Rh-C(sp²) bond and O-H bond in the rhodacycle i-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 pyrroolidine 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. On the other hand, in the cyclization of (S)-1j using (S)-H₂-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(sp²) 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.
Acknowledgements

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


[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(tBuH)(BINAP)]BARF 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-2i 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(I)(R)-H6-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-α-allyl rhodium intermediate vii was formed from vi, which was followed by carborhodation of vii and reductive elimination from vii 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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