Rhodium(I)-Catalyzed Enantioselective Cyclization of Enynes through Site-Selective C(sp³)-H Bond Activation Triggered by Formation of Rhodacycle

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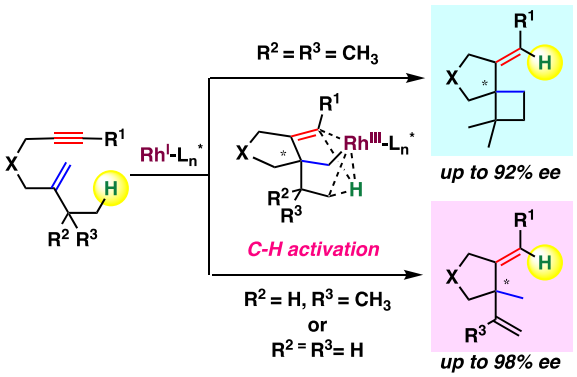

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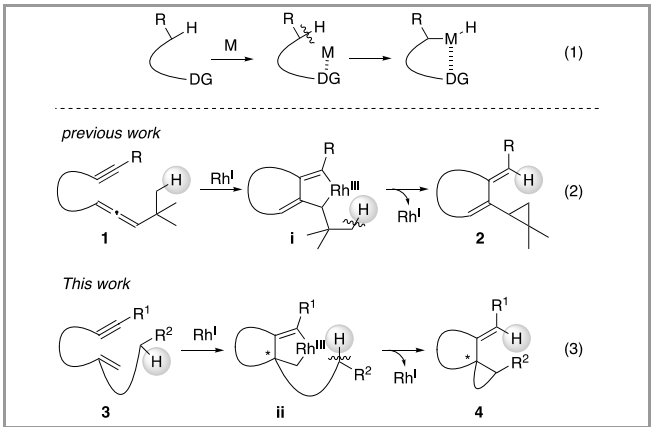
Abstract Rh(I)-catalyzed enantioselective cyclization of enyne through C(sp³)-H bond activation was investigated. It was found that the cyclization of enyne having a *t*-butyl moiety on the alkene afforded a spirocyclic compound (*up to 92% ee*), while the cyclization of enyne having an *i*-propyl or an ethyl group on the alkene gave a cyclic diene (*up to 98% ee*). Furthermore, mechanistic studies revealed that C(sp³)-H bond activation was one of the key steps in this cyclization, which had a relatively high energy barrier.

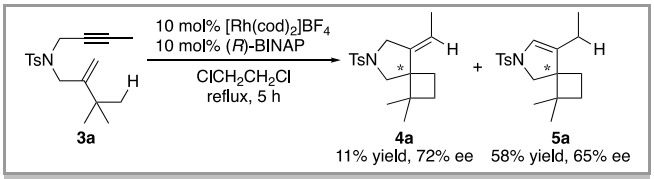
Key words rhodium, enantioselective cyclization, C(sp³)-H bond activation, alkene, alkyne, enyne

Transition metal-catalyzed aliphatic C(sp³)-H bond activations have emerged one of the most powerful and straightforward strategies for the functionalization of simple molecules in synthetic organic chemistry.[1] In general, site-selective C(sp³)-H bond activations need the assistance of directing groups (DG) containing a nitrogen or oxygen atom at the appropriate position in the substrates (Scheme 1, eq. 1).[1] On the other hand, we reported a Rh(I)-catalyzed cyclization of the substrate without directing groups through a site-selective C(sp³)-H bond activation (Scheme 1, eq. 2).[2-4] In this reaction, the rhodacycle **i** is initially formed through oxidative cycloaddition of the alkyne and the external C=C bond of the allene moiety of substrate **1** to a Rh(I) complex. By the formation of rhodacycle **i**, a C(sp³)-H bond on the *t*-butyl moiety could be close to the Rh(III) center, causing C(sp³)-H bond activation to produce the cyclic compound **2**. That is, the rhodacycle **i** acts as a directing group to lead to the site-selective C(sp³)-H bond activations. In this context, we speculated that if the enyne **3** having an 1,1-disubstituted alkene instead of allenyne **1** reacted with the chiral Rh(I) complex, the rhodacycle **ii** would be formed stereoselectively. If a C(sp³)-H bond activation occurs by rhodacycle **ii**, spirocyclic compound **4** would be formed in a stereoselective manner (Scheme 1, eq. 3). Herein, we report a Rh(I)-catalyzed enantioselective cyclization of enynes[5] through a C(sp³)-H bond activation.[6,7]



Scheme 1 Transition metal-catalyzed C(sp³)-H bond activation.

Initially, the reaction of **3a** with [Rh((*R*)-BINAP)]BF_4 (10 mol%) was carried out in $ClCH_2CH_2Cl$ at reflux (Scheme 2). As a result, the cyclization proceeded through a C(sp³)-H bond activation, giving the expected cyclic compound **4a** in 11% yield along with its isomer **5a** in 58% yield, and their ees showed 72% and 65%, respectively.[8-10]

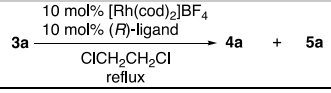


Scheme 2 Rh(I)-catalyzed enantioselective cyclization of enyne **3a** through

C(sp^3)-H bond activation.

Encouraged by this result, the cyclization of **3a** was tested using various ligands (Table 1). When (*R*)-tolBINAP was used as a ligand, the total yield of **4a** and **5a** was improved to 90% and their ees showed 85% and 81%, respectively (entry 2). The reaction of **3a** using (*R*)-H$_8$-BINAP afforded both **4a** and **5a** in 88% yield even though their ees were slightly decreased (entry 3). On the other hand, segphos-type ligands were not effective for this cyclization (entries 4 and 5).[11]

Table 1 Cyclization using various ligands.[a]



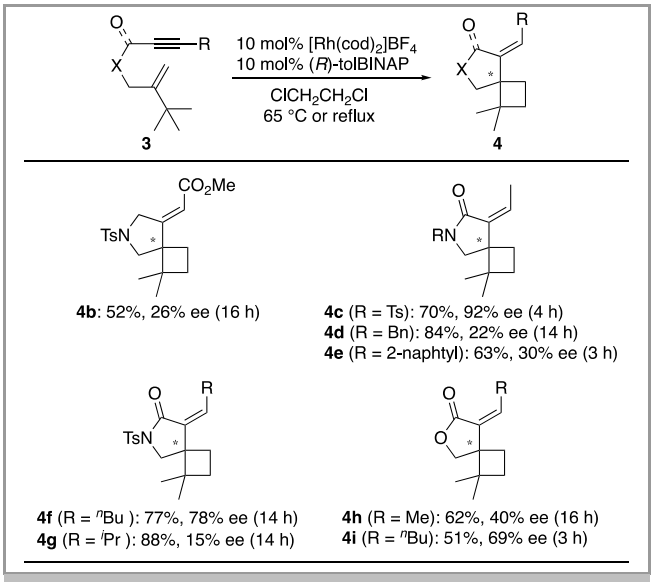
Entry	Ligand	Time (h)	Yield (%) (**4a**/**5a**)	Ratio (**4a**/**5a**)	Ee (%) (**4a**/**5a**)
1	(*R*)-BINAP	5	69	1/5.3	72/65
2	(*R*)-tolBINAP	5	90	1/1.6	85/81
3	(*R*)-H$_8$-BINAP	1	88	1/5.2	77/74
4	(*R*)-SEGPHOS	9	61	1/1/3	87/72
5	(*R*)-DTBM-SEGPHOS	19	28	2.1/1	80/N.D.[b]

[a] [Rh(cod)$_2$]BF$_4$ (0.016 mmol), ligand (0.016 mmol), **3a** (0.16 mmol), and solvent (1.6 mL) were employed. [b] N. D. = Not determined.

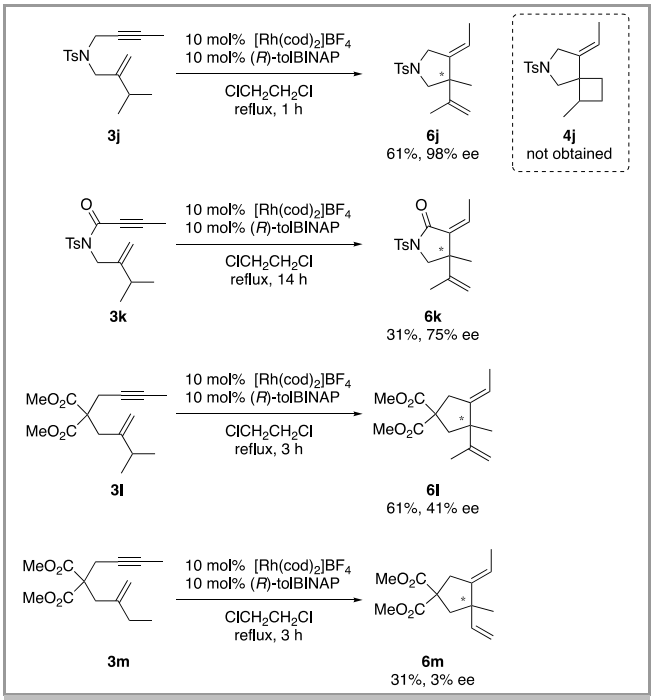
On the basis of the results shown in Table 1, we selected the conditions in entry 2 using (*R*)-tolBINAP as a ligand and investigated other substrates that were designed to avoid isomerization of the olefin in the product (Scheme 3). The cyclization of **3b** having an ester moiety on the alkyne gave the desired cyclic compound **4b** in 52 % yield as a single isomer, but the enatioselectivity was low. When the enyne **3c** having a sulfonimide moiety was employed in this reaction, the spirocyclic compound **4c** was obtained in 70% yield with high enantioselectivity (92% ee). However, the enantioselectivity was dramatically affected by both protecting groups at the nitrogen atom and substituents on the alkyne in the substrate. That is, the protecting group was changed from a tosyl group to a benzyl or a 2-naphtyl group, resulting in a decrease in the ee of the product. In addition, the cyclization of **3f** having a *n*-butyl group on the alkyne afforded **4f** with good yield, while the reaction of **3g** having an *i*-propyl group on the alkyne gave **4g** with low ee. Furthermore, this cyclization is applicable to the construction of 5-membered lactones, and **4h** and **4i** were obtained in good yields, albeit with moderate ees.

Next, enyne **3j** having an *i*-propyl group instead of a *t*-butyl group on the alkene moiety was subjected to the same reaction conditions (Scheme 4). Surprisingly, it was found that the cyclic diene **6j** instead of the expected spirocyclic compound **4j** was produced in a good yield with a high ee. The cyclization of **3k** and **3l** also afforded the cyclic dienes **6k** and **6l**, although their ees were moderate. The reaction of enyne **3m** having an ethyl group gave the cyclic compound **6m** in 31% yield with 3% ee.

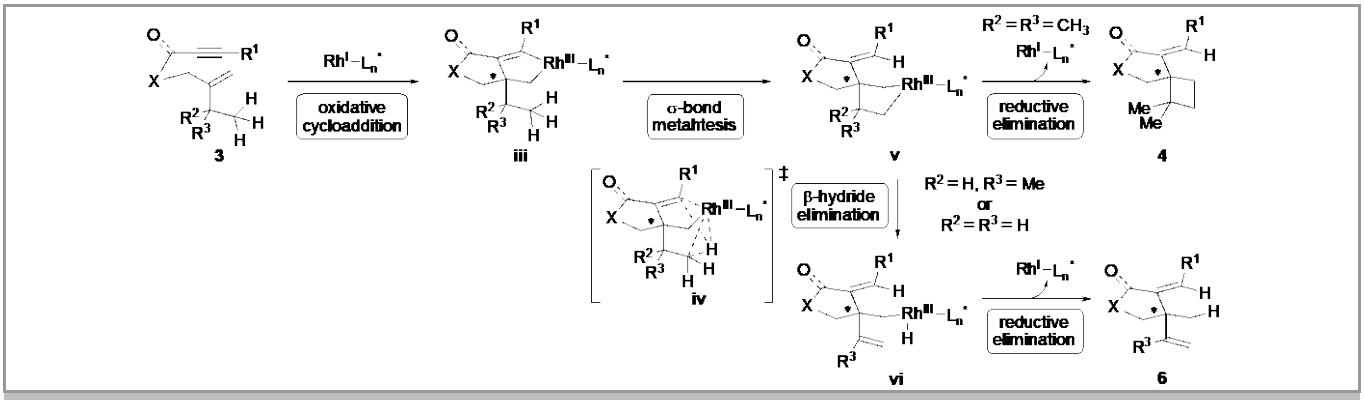
A possible reaction mechanism for the formation of **4** and **6** from **3** is depicted in Scheme 5. Initially, stereoselective oxidative cyclization of alkyne and alkene in substrate **3** to the Rh(I) complex would occur to provide the rhodacycle **iii**. By virtue of the formation of rhodacycle **iii**, a C(sp^3)-H bond on the methyl part in the *t*-butyl, *i*-propyl, or ethyl group in the substrate could be close to the cationic Rh(III) center, which would cause σ-bond metathesis such as transition state **iv** to afford the rhodacycle **v**.[12] In the case of a substrate having a *t*-butyl moiety (R^2 = R^3 = Me) on the alkene, reductive elimination from **v** occurs to give the spirocyclic compound **4** along with regeneration of the Rh(I) complex. On the other hand, in the case of a substrate having an *i*-propyl (R^2 = H, R^3 = Me) or an ethyl (R^2 = R^3 = H) moiety on the alkene, β-hydride elimination from **v** occurs more easily than reductive elimination of **4**, followed by reductive elimination from **vi** to give the cyclic diene **6** along with regeneration of the Rh(I) complex.



Scheme 3 Rh(I)-catalyzed cyclization through C(sp^3)-H bond activation of various substrates.

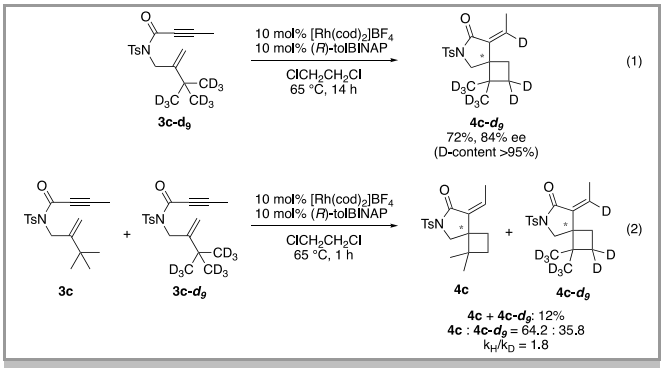


Scheme 4 Cyclization of enyne having an *i*-propyl or an ethyl moiety in the alkene.



Scheme 5 Possible reaction course.

To gain an insight into the reaction mechanism, we investigated the reaction of **3c-*d*₉** having a deuterium-labeled *t*-butyl moiety (Scheme 6). The reaction of **3c-*d*₉** under the same conditions as those in the above-mentioned reaction of **3c** (shown in Scheme 3) gave the corresponding cyclic compound **4c-*d*₉** in 72% yield with 84% ee (eq. 1), which is completely consistent with the mechanism shown in Scheme 5. Next, we performed a kinetic isotope competition experiment using an equimolar mixture of allenyne **3c** and **3c-*d*₉** (eq. 2). The reaction of a mixture of **3c** and **3c-*d*₉** (**3c**/**1c-*d*₉** = 1/1) with $[Rh(cod)_2]BF_4$ (10 mol%) and (*R*)-tolBINAP (10 mol%) at 65 °C was carried out and quenched at an early stage (1 h). As a result, it was found that the reaction gave a mixture of **4c** and **4c-*d*₉** in 12% yield in a ratio of **4c**:**4c-*d*₉** = 64.2:35.8, by which the KIE of this reaction was calculated to be approximately 1.8. Although the experimental KIE value is not high, this result suggests that cleavage of the C(sp^3)-H bond activation is one of the key steps in this cyclization, which has a relatively high energy barrier.[13]



Scheme 6 Mechanistic studies.

In conclusion, we have succeeded in the development of Rh(I)-catalyzed enantioselective cyclization of enyne through C(sp^3)-H bond activation. It was found that the cyclization of enyne having a *t*-butyl moiety on the alkene afforded a spirocyclic compound (*up to 92% ee*), while the cyclization of enyne having an *i*-propyl or an ethyl moiety on the alkene gave a cyclic diene (*up to 98% ee*). Furthermore, the results of an experiment using a deuterium-labeled substrate support our proposed mechanism depicted in Scheme 5.

All manipulations were performed under an argon atmosphere unless stated otherwise. DCE were distilled under an argon atmosphere from CaH_2. All other solvents and reagents were purified when necessary by standard procedures. Column chromatography was performed on silica gel 60 N (spherical, neutral; Kanto Kagaku, 45-50 μm), or silica gel 60 N (spherical, neutral; Kanto Kagaku, 63-210 μm) with the indicated solvent as eluent. IR spectra were obtained on a JASCO FT/IR 460Plus spectrometer. ^1H NMR spectra were recorded on JEOL ECX400P (400 MHz), JEOL ECS400 (400 MHz), and JEOL ECA500 (500 MHz) NMR spectrometer. Chemical shifts are reported in ppm from the solvent as the internal standard ($CDCl_3$: δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on JEOL ECX400P (100 MHz), JEOL ECS400 (100 MHz), and JEOL ECA500 (125 MHz) NMR spectrometer. Chemical shifts are reported in ppm from the solvent as the internal standard ($CDCl_3$: δ = 77.00 ppm). Mass spectra were obtained on JEOL JMS-T100LP and JMS-T100GCV and JEOL JMS-FAB mate mass spectrometer, and Thermo Scientific Exactive mass spectrometer. Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). Chiral HPLC analyses were carried out using a JASCO PU-980 and using indicated chiral column.

General Procedure for Cyclization Using [Rh(ligand)]BF_4

A solution of $[Rh(cod)_2]BF_4$ (0.0160 mmol, 10 mol% to a substrate) and ligand (0.0160 mmol, 10 mol% to a substrate) in degassed (Freeze-Pump up-Thaw cycle was conducted) DCE (0.62 mL: 0.026 M to Rh) was stirred under H_2 atmosphere at room temperature for 1 h. Then the reaction mixture was degassed, and the reaction vessel was flushed with Ar gas. To the mixture was added a solution of substrate (0.160 mmol) in degassed DCE (0.98 mL) and the reaction mixture was stirred at 65 °C or reflux until the substrate disappeared on TLC. After removal of the solvent, the residue was purified by column chromatography on silica gel to give product.

(*Z*)-8-Ethylidene-1,1-dimethyl-6-tosyl-6-azaspiro[3.4]octane (4a) and 8-Ethyl-1,1-dimethyl-6-tosyl-6-azaspiro[3.4]oct-7-ene (5a)

According to the general procedure for cyclization, a crude product, which was prepared from **3a** (51.2 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.5 mg, 0.0160 mmol) and (*R*)-tolBINAP (10.8 mg, 0.0160 mmol) in DCE (1.60 mL) at reflux for 5 h, was purified by column chromatography on silica gel (benzene) to give **4a** (17.9 mg, 35% yield, 85% ee) and **5a** (28.1 mg, 55% yield, 81% ee) as a colorless oil.

4a

$[\alpha]_D^{20}$ = +13.5 (*c* 0.90, $CHCl_3$, 85% ee); HPLC (DAICEL CHIRALPAK AS-H; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 19.7 (major), 24.6 (minor) min.

IR (neat): 3019, 2924, 1597, 1463, 1215, 759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.36 (m, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.80 (m, 1H), 3.57 (m, 1H), 2.48 (d, *J* = 9.2 Hz, 1H), 2.42 (s, 3H), 1.86 (m, 1H), 1.73 (m, 1H), 1.59 (m, 5H), 1.12 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.4, 139.5, 132.7, 129.6, 127.8, 116.5, 54.8, 52.9, 49.8, 41.0, 30.5, 25.4, 24.7, 22.5, 21.5, 14.2.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{25}NO_2S$: 319.1606; found: 319.1600.

5a

$[\alpha]_D^{20}$ = -4.61 (*c* 1.05, $CHCl_3$, 81% ee); HPLC (DAICEL CHIRALPAK AS-H; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 27.5 (minor), 30.8 (major) min.

IR (neat): 3023, 2925, 1731, 1345, 1163 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.07 (t, *J* = 1.8 Hz, 1H), 3.77 (d, *J* = 11.3 Hz, 1H), 2.95 (d, *J* = 11.3 Hz, 1H), 2.41 (s, 3H), 2.22 (m, 2H), 1.88 (m, 1H), 1.69 (m, 2H), 1.43 (m, 1H), 1.10 (t, *J* = 7.2 Hz, 3H), 0.95 (s, 3H), 0.59 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.8, 133.9, 132.7, 129.8, 128.0, 124.2, 56.4, 56.2, 42.2, 31.9, 27.1, 27.0, 24.5, 21.8, 20.3, 12.6.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{25}NO_2S$: 319.1606; found: 319.1600.

Methyl (*Z*)-2-(1,1-dimethyl-6-tosyl-6-azaspiro[3.4]octan-8-ylidene)acetate (4b)

According to the general procedure for cyclization, a crude product, which was prepared from **3b** (58.3 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.6 mg, 0.0160 mmol) and (*R*)-tolBINAP (10.0 mg, 0.0160 mmol) in DCE (1.60 mL) at 65 °C for 16 h, was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give **4b** (30.2 mg, 52% yield, 26% ee) as a colorless oil.

$[\alpha]_D^{20}$ = +28.5 (*c* 1.21, $CHCl_3$, 26% ee); HPLC (DAICEL CHIRALPAK IA-3; *n*-hexane/2-propanol, 95/5; 1.0 mL/min; λ = 256 nm): t_R = 8.3 (major), 9.9 (minor) min.

IR (neat): 2954, 2255, 1710, 1355, 1164, 909, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.71 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 5.80 (t, *J* = 2.5 Hz, 1H), 4.32 (dd, *J* = 18.0, 2.5 Hz, 1H), 4.01 (dd, *J* = 18.0, 2.5 Hz, 1H), 3.92 (d, *J* = 10.0 Hz, 1H), 3.69 (s, 3H), 2.46 (d, *J* = 10.0 Hz, 1H), 2.41 (s, 3H), 1.88 (m, 2H), 1.67 (m, 2H), 1.24 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 162.4, 143.7, 132.0, 129.7, 128.0, 112.0, 54.8, 53.6, 52.6, 51.4, 42.6, 30.5, 25.4, 24.9, 22.4, 21.5.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{19}H_{25}NO_4S$: 363.1504; found: 363.1498.

(*Z*)-8-Ethylidene-1,1-dimethyl-6-tosyl-6-azaspiro[3.4]octan-7-one (4c)

According to the general procedure for cyclization, a crude product, which was prepared from **3c** (53.5 mg, 0.161 mmol) and $[Rh(cod)_2]BF_4$ (6.5 mg, 0.0160 mmol) and (*R*)-tolBINAP (10.6 mg, 0.0156 mmol) in DCE (1.60 mL) at 65 °C for 14 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to give **4c** (37.7 mg, 70% yield, 92% ee) as a white solid.

Mp. 108-111 °C.

$[\alpha]_D^{23}$ = -14.2 (*c* 1.04, $CHCl_3$, 92% ee); HPLC (DAICEL CHIRALPAK IA-3; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 256 nm): t_R = 11.4 (minor), 15.3 (major) min.

IR (neat): 3024, 2925, 1822, 1363, 1170 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.15 (q, *J* = 7.2 Hz, 1H), 4.34 (d, *J* = 10.0 Hz, 1H), 3.35 (d, *J* = 10.0 Hz, 1H), 2.43 (s, 3H), 2.18 (d, *J* = 7.2 Hz, 3H), 2.06 (m, 1H), 1.81 (m, 1H), 1.68 (m, 2H), 1.23 (m, 3H), 0.78 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 144.9, 137.3, 135.5, 133.8, 129.6, 128.0, 52.1, 48.8, 41.9, 30.6, 25.2, 24.8, 24.6, 21.7, 13.7.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{23}O_3NNaS$: 356.1291; found: 356.1286.

(*Z*)-6-Benzyl-8-ethylidene-1,1-dimethyl-6-azaspiro[3.4]octan-7-one (4d)

According to the general procedure for cyclization, a crude product, which was prepared from **3d** (46.2 mg, 0.171 mmol) and $[Rh(cod)_2]BF_4$ (6.7 mg, 0.0165 mmol) and (*R*)-tolBINAP (10.6 mg, 0.0155 mmol) in DCE (1.60 mL) at reflux for 14 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to give **4d** (38.6 mg, 84% yield, 22% ee) as a colorless oil.

$[\alpha]_D^{20}$ = -6.16 (*c* 0.79, $CHCl_3$, 22% ee); HPLC (DAICEL CHIRALPAK IA-3; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 9.9 (minor), 11.7 (major) min.

IR (neat) 2967, 1682, 1656 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5H), 6.06 (q, *J* = 8.8 Hz, 1H), 4.69 (d, *J* = 15.2 Hz, 1H), 4.26 (d, *J* = 15.2 Hz, 1H), 3.49 (d, *J* = 10.0 Hz, 1H), 2.92 (d, *J* = 10.0 Hz, 1H), 2.33 (d, *J* = 8.8 Hz, 3H), 2.01 (m, 1H), 1.81 (m, 1H), 1.61 (m, 2H), 0.91 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0, 136.7, 135.7, 131.3, 128.5, 128.4, 127.5, 52.1, 48.6, 46.3, 41.8, 31.0, 25.4, 25.3, 25.1, 13.2.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{23}NO$: 269.1780 found: 269.1782.

(*Z*)-8-Ethylidene-1,1-dimethyl-6-(naphthalen-2-ylmethyl)-6-azaspiro[3.4]octan-7-one (4e)

According to the general procedure for cyclization, a crude product, which was prepared from **3e** (51.1 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.8 mg, 0.0167 mmol) and (*R*)-tolBINAP (10.9 mg, 0.0161 mmol) in DCE (1.60 mL) at reflux for 3 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to give **4e** (32.2 mg, 63% yield, 30% ee) as a colorless oil.

$[\alpha]_D^{20}$ = +0.77 (*c* 0.82, $CHCl_3$, 30% ee); HPLC (DAICEL CHIRALPAK IA-3; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 10.5 (minor), 12.9 (major) min.

IR (neat): 2952, 2860, 1684, 1660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (m, 3H), 7.69 (s, 1H), 7.48 (m, 2H), 7.36 (d, *J* = 1.2 Hz, 1H), 6.06 (q, *J* = 7.6 Hz, 1H), 4.84 (d, *J* = 14.8 Hz, 1H), 4.39 (d, *J* = 14.8 Hz, 1H), 3.49 (d, *J* = 6.4 Hz, 1H), 2.91 (d, *J* = 6.4 Hz, 1H), 2.34 (d, *J* =7.6 Hz, 3H), 2.01 (m, 1H), 1.77 (m, 1H), 1.56 (m, 2H), 0.91 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 135.6, 134.2, 133.2, 132.8, 131.4, 128.4, 127.7, 127.6, 127.0, 126.3, 126.2, 125.9, 52.2, 48.6, 46.4, 41.8, 30.9, 25.5, 25.3, 25.1, 13.3.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{22}H_{25}NO$: 319.1936; found: 319.1926.

(*Z*)-1,1-imethyl-8-pentylidene-6-tosyl-6-azaspiro[3.4]octan-7-one (4f)

According to the general procedure for cyclization, a crude product, which was prepared from **3f** (60.0 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.7 mg, 0.0165 mmol) and (*R*)-tolBINAP (10.8 mg, 0.0159 mmol) in DCE (1.60 mL) at reflux for 14 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to give **4f** (46.1 mg, 77% yield, 78% ee) as a colorless oil.

$[\alpha]_D^{20}$ = -49.9 (*c* 1.32, $CHCl_3$, 78% ee); HPLC (DAICEL CHIRALPAK IA-3; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 7.3 (minor), 8.6 (major) min.

IR (neat): 2924, 1724, 1462, 1364 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.03 (t, *J* = 8.0 Hz, 1H), 4.33 (d, *J* = 10.0 Hz, 1H), 3.33 (d, *J* = 10.0 Hz, 1H), 2.78 (m, 1H), 2.58 (m, 1H), 2.42 (s, 3H), 2.05 (m, 1H), 1.78 (m, 1H),

1.69 (m, 1H), 1.60 (m, 1H), 1.33 (m, 4H), 1.09 (s, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 144.8, 143.1, 135.5, 132.7, 129.6, 128.0, 52.1, 48.7, 41.8, 31.6, 30.6, 27.0, 25.2, 24.8, 24.5, 22.4, 21.6, 13.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{29}O_3NNaS$: 398.1760; found: 398.1760.

(*Z*)-1,1-Dimethyl-8-(2-methylpropylidene)-6-tosyl-6-azaspiro[3.4]octan-7-one (4g)

According to the general procedure for cyclization, a crude product, which was prepared from **3g** (56.9 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.7 mg, 0.0165 mmol) and (*R*)-tolBINAP (10.8 mg, 0.0159 mmol) in DCE (1.60 mL) at reflux for 14 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to give **4g** (50.0 mg, 88% yield, 15% ee) as a colorless oil.

$[\alpha]_D^{20}$ = -13.8 (*c* 1.02, $CHCl_3$, 15% ee); HPLC (DAICEL CHIRALPAK IA-3; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 6.6 (minor), 7.7 (major) min.

IR (neat): 3025, 2960, 2864, 1721, 1362, 1169 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.82 (d, *J* = 10.0 Hz, 1H), 4.33 (d, *J* = 10.0 Hz, 1H) , 3.71 (m, 1H), 3.32 (d, *J* = 10.0 Hz, 1H), 2.41 (s, 3H), 2.03 (m, 1H), 1.80 (m, 1H), 1.67 (m, 1H), 1.60 (m, 1H), 1.08 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 149.6, 144.9, 135.4, 130.7, 129.6, 128.0, 52.1, 48.4, 41.8, 30.5, 26.0, 25.1, 24.8, 24.3, 22.8, 22.7, 21.7.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{27}O_3NNaS$: 384.1604; found: 384.1598.

(*Z*)-8-Ethylidene-1,1-dimethyl-6-oxaspiro[3.4]octan-7-one (4h)

According to the general procedure for cyclization, a crude product, which was prepared from **3h** (29.0 mg, 0.161 mmol) and $[Rh(cod)_2]BF_4$ (6.5 mg, 0.0160 mmol) and (*R*)-tolBINAP (10.8 mg, 0.0159 mmol) in DCE (1.60 mL) at 65 °C for 16 h, was purified by column chromatography on silica gel (benzene) to give **4h** (18.0 mg, 62% yield, 40% ee) as a colorless oil.

$[\alpha]_D^{20}$ = -141.7 (*c* 0.72, $CHCl_3$, 40% ee); HPLC (DAICEL CHIRALPAK OJ-H; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 5.4 (major), 6.7 (minor) min.

IR (neat): 2959, 2925, 1755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (q, *J* = 7.2 Hz, 1H), 4.63 (d, *J* = 9.6 Hz, 1H), 3.83 (d, *J* = 9.6 Hz, 1H), 2.26 (d, *J* = 7.2 Hz, 3H), 2.06 (m, 1H), 1.87 (m, 1H), 1.66 (t, *J* = 7.6 Hz, 2H), 1.15 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 138.0, 130.2, 72.4, 51.3, 41.5, 30.6, 25.2, 25.1, 24.4, 13.9.

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{11}H_{16}O_2$: 180.1150; found: 180.1145.

(*Z*)-1,1-Dimethyl-8-pentylidene-6-oxaspiro[3.4]octan-7-one (4i)

According to the general procedure for cyclization, a crude product, which was prepared from **3i** (35.1 mg, 0.158 mmol) and $[Rh(cod)_2]BF_4$ (6.7 mg, 0.0165 mmol) and (*R*)-tolBINAP (10.9 mg, 0.0161 mmol) in DCE (1.60 mL) at 65 °C for 3 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 9:1) to give **4i** (17.9 mg, 51% yield, 69% ee) as a colorless oil.

$[\alpha]_D^{20}$ = -51.7 (*c* 1.08, $CHCl_3$, 69% ee); HPLC (DAICEL CHIRALPAK OD-H; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 3.7 (minor), 4.2 (major) min.

IR (neat): 2952, 2927, 1754, 1462, 1363, 1114 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.21 (t, *J* = 7.5 Hz, 1H), 4.62 (d, *J* = 9.0 Hz, 1H), 3.83 (d, *J* = 9.0 Hz, 1H), 2.84 (m, 1H), 2.72 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.66 (t, *J* = 7.0 Hz, 2H), 1.49 (tt, *J* = 7.0, 7.0 Hz, 2H), 1.40 (qt, *J* = 7.0, 7.0 Hz, 2H), 1.15 (s, 3H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.92 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ =170.7, 143.9, 129.4, 72.6, 51.5, 41.7, 31.8, 30.9, 27.5, 25.5, 25.4, 24.6, 22.7, 14.2.

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{14}H_{22}O_2$: 222.1620; found: 222.1614.

(*Z*)-4-Ethylidene-3-methyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine (6j)

According to the general procedure for cyclization, a crude product, which was prepared from **3j** (48.9 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.5 mg, 0.0160 mmol) and (*R*)-tolBINAP (10.6 mg, 0.0156 mmol) in DCE (1.60 mL) at reflux for 1 h, was purified by column chromatography on silica gel (benzene) to give **6j** (29.8 mg, 61% yield, 98% ee) as a colorless oil.

$[\alpha]_D^{20}$ = -3.20 (*c* 0.91, $CHCl_3$, 98% ee); HPLC (DAICEL CHIRALPAK AS-H; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 19.9 (minor), 23.4 (major) min.

IR (neat) 3019, 1216, 762 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.17 (m, 1H), 4.84 (s, 1H), 4.81 (s, 1H), 3.82 (m, 2H), 3.46 (d, *J* = 9.0 Hz, 1H), 2.84 (d, *J* = 9.0 Hz, 1H), 2.43 (s, 3H), 1.62 (s, 3H), 1.55 (dd, *J* = 7.0, 2.0 Hz, 3H), 1.16 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 143.5, 141.7, 133.0, 129.6, 127.7, 117.1, 112.3, 58.0, 50.7, 49.6, 23.9, 21.5, 19.4, 14.4.

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{17}H_{23}NO_2S$: 305.1450; found: 305.1450.

(*Z*)-3-Ethylidene-4-methyl-4-(prop-1-en-2-yl)-1-tosylpyrrolidin-2-one (6k)

According to the general procedure for cyclization, a crude product, which was prepared from **3k** (51.1 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.5 mg, 0.0160 mmol) and (*R*)-tolBINAP (10.6 mg, 0.0156 mmol) in DCE (1.60 mL) at reflux for 1 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 15:1) to give **6k** (15.6 mg, 31% yield, 75% ee) as a colorless oil.

$[\alpha]_D^{20}$ = -6.60 (*c* 1.34, $CHCl_3$, 75% ee); HPLC (DAICEL CHIRALPAK IA-3; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 11.0 (minor), 11.9 (major) min.

IR (neat): 2925, 2854, 1719, 1460, 1376 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 5.95 (q, *J* = 7.0 Hz, 1H), 4.87 (t, *J* = 2.0 Hz, 2H), 3.88 (d, J = 9.5 Hz, 1H), 3.49 (d, *J* = 9.5 Hz, 1H), 2.43 (s, 3H), 2.12 (d, *J* = 7.0 Hz, 3H), 1.63 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 146.6, 145.0, 138.6, 136.1, 135.4, 129.6, 128.1, 113.2, 54.8, 45.3, 25.7, 21.7, 19.3, 13.7.

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{17}H_{21}NO_3S$: 319.1242; found: 319.1247.

(*E*)-Dimethyl-4-ethylidene-3-methyl-3-(prop-1-en-2 yl)cyclopentane-1,1-dicarboxylate (6l)

According to the general procedure for cyclization, a crude product, which was prepared from **3l** (42.6 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.5 mg, 0.0160 mmol) and (*R*)-tolBINAP (10.6 mg, 0.0156 mmol) in DCE (1.60 mL) at reflux for 1 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 15:1) to give **6l** (26.0 mg, 61% yield, 41% ee) as a colorless oil.

$[\alpha]_D^{20}$ = -6.32 (*c* 1.41, $CHCl_3$, 41% ee); HPLC (DAICEL CHIRALPAK OJ-H; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 207 nm): t_R = 9.8 (major), 12.0 (minor) min.

IR (neat): 2954, 1737, 1435, 1255 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.17 (m, 1H), 4.69 (s, 2H), 3.71 (s, 6H), 3.06 (d, *J* = 17.0 Hz, 1H), 2.97 (d, *J* = 17.0 Hz, 1H), 2.73 (d, *J* = 14.0 Hz, 1H), 2.08 (d, *J* = 14.0 Hz, 1H), 1.68 (s, 3H), 1.63 (d, *J* = 4.0 Hz, 3H), 1.16 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 172.2, 149.5, 145.2, 117.2, 111.5, 57.8, 52.8, 52.5, 51.5, 45.0, 37.1, 26.0, 19.1, 14.4.

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{15}H_{22}O_4$: 266.1518; found: 266.1513.

Dimethyl (*E*)-4-ethylidene-3-methyl-3-vinylcyclopentane-1,1-dicarboxylate (6m)

According to the general procedure for cyclization, a crude product, which was prepared from **3m** (40.4 mg, 0.160 mmol) and $[Rh(cod)_2]BF_4$ (6.7 mg, 0.0165 mmol mmol) and (*R*)-tolBINAP (10.7 mg, 0.0160 mmol) in DCE (1.60 mL) at reflux for 4 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 15:1) to give **6m** (12.5 mg, 31% yield, 3% ee) as a colorless oil.

$[\alpha]_D^{20}$ = +0.93 (*c* 0.98, $CHCl_3$, 3% ee); HPLC (DAICEL CHIRALPAK OJ+OJ-H; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 225 nm): t_R = 29.4 (minor), 32.1 (major) min.

IR (neat): 2955, 1736, 1435, 1262 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.72 (dd, *J* = 18.0, 11.0 Hz, 1H), 5.19 (m, 1H), 4.89 (m, 2H), 3.70 (d, *J* = 18.0 Hz, 6H), 3.06 (d, *J* = 17.0 Hz, 1H), 2.99 (d, *J* = 17.0 Hz, 1H), 2.52 (d, *J* = 17.0 Hz, 1H), 2.24 (d, *J* = 17.0 Hz, 1H), 1.64 (d, *J* = 5.6 Hz, 3H), 1.16 (*s*, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 172.2, 145.7, 144.8, 117.2, 111.5, 57.9, 52.8, 52.7, 48.5, 46.9, 36.9, 26.0, 14.5.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{14}H_{20}O_4$: 252.1361; found: 252.1356.

(*Z*)-8-(Ethylidene-1-*d*)-1,1-bis(methyl-d_3)-6-tosyl-6-azaspiro[3.4]octan-7-one-2,2-d_2 (4c-d_9)

According to the general procedure for cyclization, a crude product, which was prepared from **3c-d_9** (55.0 mg, 0.161 mmol) and $[Rh(cod)_2]BF_4$ (6.5 mg, 0.0160 mmol) and (*R*)-tolBINAP (10.6 mg, 0.0156 mmol) in DCE (1.60 mL) at 65 °C for 14 h, was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to give **4c-d_9** (39.5 mg, 72% yield, 84% ee) as a white solid.

Mp. 103-107 °C.

$[\alpha]_D^{20}$ = -29.6 (*c* 1.62, $CHCl_3$, 84% ee); HPLC (DAICEL CHIRALPAK IA-3; *n*-hexane/2-propanol, 99/1; 1.0 mL/min; λ = 256 nm): t_R = 11.4 (minor), 15.3 (major) min.

IR (neat): 2925, 2219, 1721, 1363, 1170 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.31 (d, *J* = 10.0 Hz, 1H), 3.34 (d, *J* = 10.0 Hz, 1H), 2.42 (s, 3H), 2.16 (s, 3H), 2.03 (d, *J* = 12.0 Hz, 1H), 1.80 (d, *J* = 12.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ =166.3, 144.5, 136.6 (t, *J* = 21 Hz), 135.3, 133.5, 129.3, 127.7, 51.8, 48.5, 41.0, 29.4 (m), 24.1, 24.0 (m), 24.0 (m), 21.4, 13.4.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{14}D_9NO_3S$: 342.1964; found: 342.1953.

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Supporting Information

Is there **Supporting Information** to be published? Click here to indicate YES or NO (text and links will be updated prior to publication).

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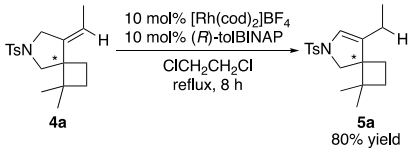
(8) The geometry of alkene in the cyclic compound **4a** was determined by NOESY. The absolute configuration of **4a** and **5a** was not determined.

(9) **4a** was subjected to the standard reaction conditions, giving **5a** in 80% yield.



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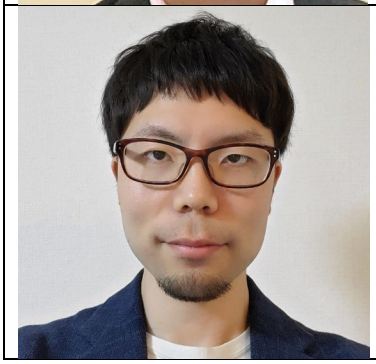
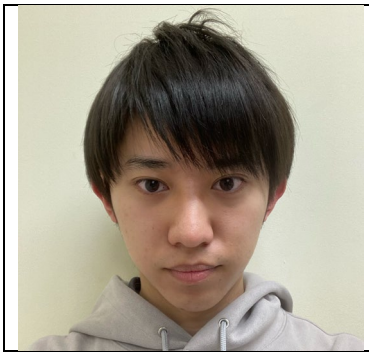
(11) The effect of the counter anion (X) of a cationic Rh(I) complex on the reactivity was investigated using a [Rh(cod)$_2$]X (X = ClO_4, PF_6, SbF_6, and BAr^F_4). However, these anions showed almost same reactivity as those using BF_4 in this cyclization.

(12) Huang studied on the mechanism for Rh(I)-catalyzed cyclization of allenyne through C(sp^3)-H bond activation[2] by means of DFT calculation. According to this paper, the cyclization proceeded through metal-assisted σ-bond metathesis like rhodacycle **iv**, see: Huang, G. *Org. Lett.* **2015**, *17*, 1994.

(13) For recent review, see: (a) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, *111*, 4857. For an essay, see: (b) Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.

Biosketches

	Yoshihiro Sato received his master degree of Pharmaceutical Sciences from Hokkaido University in 1990, and joined the faculty of Pharmaceutical Sciences, Hokkaido University as a Research Associate. He received his Ph.D. degree in 1993 from Hokkaido University under the supervision of Professors Masakatsu Shibasaki and Miwako Mori, then was promoted to an Assistant Professor. After post-doctoral research at Stanford University (Prof. P. A. Wender's group) from 1997 to 1998, he became a Lecturer at Hokkaido University in 1999 and an Associate Professor in 2001. In 2004, he was promoted to Full Professor of Hokkaido University. His research interests lie in organometallic chemistry directed towards organic synthesis, including development of new reaction and utilization of CO_2 as a C1 unit.
	Yoshihiro Oonishi received his PhD degree in 2005 from Hokkaido University under the supervision of Prof. Yoshihiro Sato. In 2005, he joined the Faculty of Pharmaceutical Sciences of Hokkaido University as a Research Associate and then became an Assistant Professor in 2007. In 2012-2013, he had the opportunity to study at University of St Andrews as a postdoctoral fellow under the supervision of Prof. Steven. P. Nolan and then returned to Hokkaido University to continue his research. Since 2016, he has been an associate professor at Hokkaido University.
	Shunki Sakamoto received his master degree in 2016 from Hokkaido University under the direction of Prof. Yoshihiro Sato. Since 2016, he has been working in Shionogi & Co., Ltd. .



Shuya Agata was born in 1998. He studied organic chemistry at Hokkaido University and joined Prof. Sato's group in 2020 as an undergraduate student.