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Effective Chirality Transfer in [3+2] Reaction between Allenyl-Rhodium and Enal: Mechanistic Study Based on DFT Calculations

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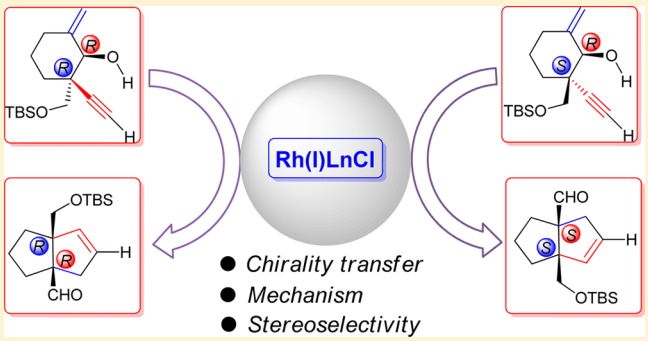
Supporting Information

ABSTRACT: Theoretical calculation was performed to study the chirality transfer in a newly reported intramolecular [3+2] cycloaddition of enal and alleno rhodium species, generated *in situ* from an enynol precursor. [3.3.0] bicyclic system which contains two bridgehead quaternary carbons that can be achieved, the chirality of which are controlled by those of the starting material, and the product stereoselectivity is only determined by the α-position of the acetylene moiety. Density functional theory calculations predicted that only the *cis* [3.3.0] bicyclic product could be generated, regardless of either *erythro* or *threo* substrate, which was also confirmed by experimental observations.

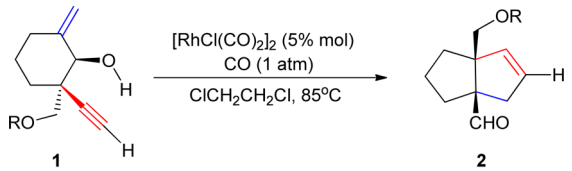


INTRODUCTION

The construction of [3.3.0] and [4.3.0] bicyclic all-carbon frameworks has attracted increasing attention in synthetic organic chemistry as well as medicinal chemistry.[1] New synthetic strategies and methodologies for this type of bicyclic rings are frequently reported for the construction of natural products and the synthesis of new therapeutic agents and drugs.[2] The preparation of these frameworks containing vicinal bridgehead quaternary carbon centers, however, remains a challenge,[3] and only a few methods were reported in the past two decades.[4] As far as we know, rare efficient synthetic approaches have been reported for the enantioselective construction of [3.3.0] and [4.3.0] bicyclic rings bearing two quaternary bridgehead carbon centers, despite the importance of this type of fragment in drug development.[5]

Recently, we reported a novel [3+2] cycloaddition of enal with alleno rhodium species, generated *in situ* from an enynol via a retro metal propargylation reaction, which can furnish [3.3.0] and [4.3.0] bicyclic systems with two quaternary bridgehead carbons (Scheme 1).[6] Notably, when chiral starting materials are employed, enantiomerically pure [3.3.0] and [4.3.0] bicyclic compounds can be achieved via this unprecedented reaction, the key structural factors of which are significant in naturally occurring, biologically active chiral molecules. As shown in Scheme 1, when (1*R*,2*R*)-enynol **1** is used as the substrate, the [3.3.0] bicyclic product **2** is generated in good yield under the optimized reaction conditions.

Scheme 1. Intramolecular [3+2] Cycloaddition of in situ Generated Allenyl−Rhodium and Enol Using (1*R*,2*R*)-Enynol 1



Although some intermediates of this novel transformation have been proposed and briefly calculated by us, the mechanistic insights of this reaction remain unclear, especially the chirality transfer in this process.[6] As shown in Scheme 2, we propose a mechanism involving two possible pathways (Pathway A and Pathway B), both of which start commonly from Rh(I)LnCl. In Pathway A, an intramolecular 3,3-sigmatropic migration of **I** generates intermediate **II**, containing an enolate moiety and a rhodium-coordinated chiral allene moiety. A Conia-ene-type reaction[7] between these two moieties then gives intermediate **III**. Finally, product **2** is generated by protonalysis[8] with substrate **1**, and complex **I** is regenerated, completing the catalytic cycle. In Pathway B, a retro propargylation reaction[9] of

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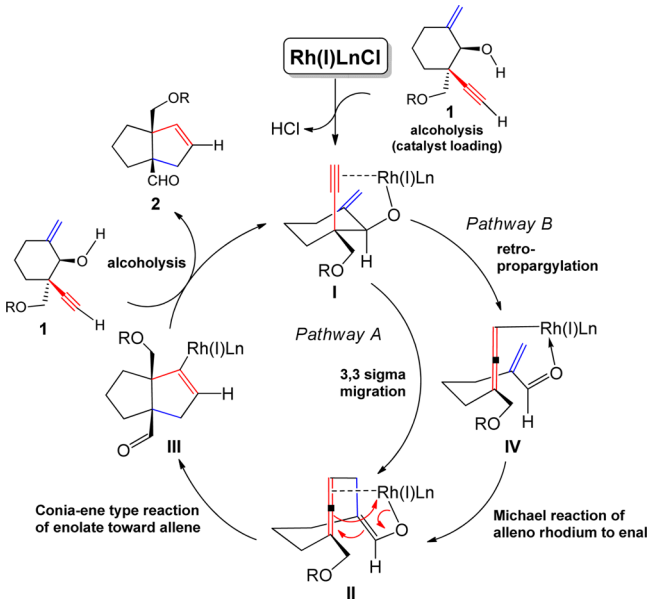
Scheme 2. Proposed Reaction Pathways A and B



I generates alleno−rhodium **IV**. Alternatively, intermediate **II** can be also generated by intramolecular Michael-type addition of the alleno−rhodium to enal moiety in **IV**. In both pathways, the chiral center in substrate enynol **1** could be effectively transferred to the vicinal quaternary carbon centers in product **2**.[10]

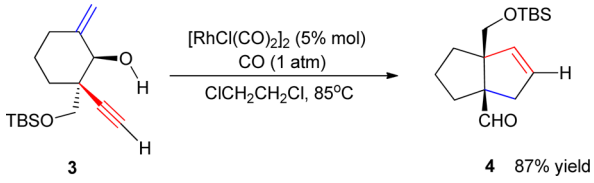
COMPUTATIONAL METHODS

Density functional theory (DFT) investigations were performed to elucidate the mechanism of this newly reported intramolecular [3+2] reaction, and to reveal the fundamental differences among the diastereoisomeric substrates to clarify the stereochemistry. Geometry optimization and harmonic vibration frequency calculation were carried out using the M11-L functional,[11] and a mixed basis set (LANL08[12] for rhodium and 6-311+G(d)[13] for other atoms). The solvent effects were calculated by single point energy (SPE) calculations on the corresponding gas-phase stationary points with a SMD continuum solvation model.[14] The energies given in this work are M11-L calculated Gibbs free energies, which could give more accurate energetic information,[15] in 1,2-dichloroethane solvent. All the calculations were carried out using Gaussian 09 series of programs.[16]

RESULTS AND DISCUSSION

To elucidate the mechanism of the asymmetric synthesis, a *tert*-butyldimethylsilyl-substituted (1*R*,2*R*)-enynol **3** was selected as the substrate (Scheme 3). Computational results for these two possible mechanisms are summarized in Figure 1.

Scheme 3. Intramolecular [3+2] Reaction of in situ Generated Allenyl−Rhodium and Enol Using (1*R*,2*R*)-Enynol 3



As shown in Figure 1, **CP1**, which is formed by initiation of a dicarbonyl−rhodium complex with **3**, is chosen as the relative zero point for the free-energy profiles of these catalytic cycles. In Pathway A, the intramolecular 3,3-sigmatropic migration from **CP1** to **CP2** takes place via a concerted transition state **TS1**; activation free energy for this step is 19.3 kcal/mol. The geometric information for **TS1** is shown in Figure 1. The lengths of the forming C−C and breaking C−C bonds are 2.00 and 1.64 Å, respectively, which indicate a concerted process. The allene moiety in **CP2** is activated by its coordination to the rhodium center. Subsequent alkylation of enolate by the activated allene occurs via a Conia-ene-type reaction. This alkylation step via **TS2** is facile and could afford the intramolecular [3+2] cycloadduct **CP3**, with an activation free energy of 7.2 kcal/mol. The demetalation step proceeds with ligand exchange between aldehyde moiety in **CP3** and the starting material **3**. Then, the C−Rh bond in generated **CP4** is protonated via a four-membered-ring transition state **TS3**. Along with the release of product **4**, the active intermediate **CP1** is regenerated irreversibly to complete the catalytic cycle.

In Pathway B, intramolecular retro metal propargylation from **CP1** to **CP5** takes place via transition state **TS4** with an energy barrier of 16.9 kcal/mol. The geometric information for **TS4** is shown in Figure 1. The lengths of the breaking C−C and forming C−Rh bonds are 2.02 and 2.18 Å, respectively. The allene−rhodium complex **CP5** is then formed reversibly, in which the chirality of the allene is determined by the α-carbon of the acetylene moiety in **CP1**. In **CP5**, the enone moiety is activated by the linked rhodium atom, because the oxygen atom in this moiety coordinates to rhodium. Subsequent Michael-type addition of alleno−rhodium to the activated enone via **TS5** generates **CP2** with an activation free energy of 24.4 kcal/mol, which is 5.1 kcal/mol higher than that of **TS1**. Theoretical calculations indicated that the mechanism of 3,3-sigmatropic is favorable. This mechanism including 3,3-sigmatropic migration and Conia-ene type reaction accounts for how the chirality in the reactant can be transferred to the final [3+2] cycloadduct. The present [3+2] reaction is a new type of allene reaction, and its mechanism is different from those of previously reported [3+2] reactions of allenylsilanes and allenoates.

We also tried to predict the stereoselectivity when (1*R*,2*S*)-enynol **5**, a diastereoisomer of (1*R*,2*R*)-enynol **3**, is used as the substrate. In this case, when **CP6** is set to the initial species, the corresponding 3,3-sigmatropic migration could not take place because the equatorial acetylene moiety is far away from olefin moiety in **CP6**. Therefore, only pathway B is considered in this case.

As shown in Figure 2 (black lines), **CP6**, which is chosen as the relative zero point for the free-energy profiles of these catalytic cycles, is formed by initiation of a dicarbonyl−rhodium complex with enynol **5**. An intramolecular retro metal propargylation takes place via a concerted transition state **TS6** with an 11.2 kcal/mol barrier. Allene−rhodium complex **CP7** is formed reversibly, and the chirality of the formed allene moiety is the opposite of that in **CP5**. **CP7** can isomerize to **CP8** with 2.4 kcal/mol endothermic. In **CP8**, the oxygen atom in the enone moiety coordinates with rhodium. Subsequently, Michael-type addition can occur through transition state **TS7**, with a barrier of 16.9 kcal/mol, generating the *cis* eight-membered-ring intermediate **CP9**. The geometric information for **TS7** is shown in Figure 2. The lengths of the forming C−C and breaking C−Rh bonds are 2.18 and 2.19 Å, respectively. The allene chirality would be conserved in **TS7** and the subsequent

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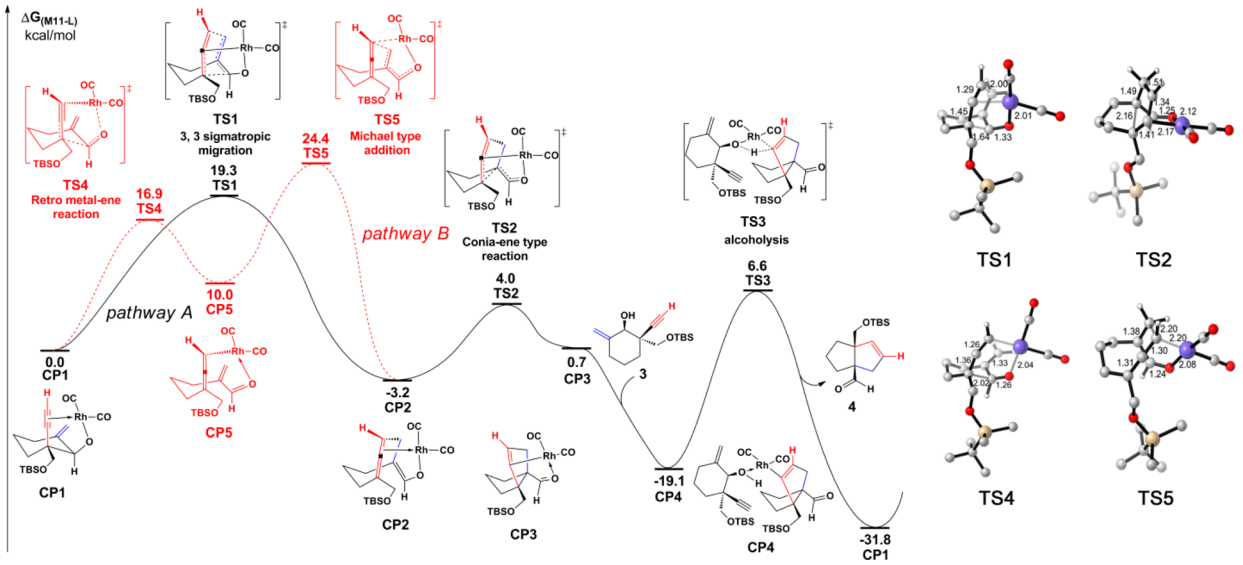

Figure 1. Gibbs free energy profiles and structural information for two possible pathways of rhodium-catalyzed synthesis of bicyclic octane **4**. The values of bond lengths are given by angstrom.

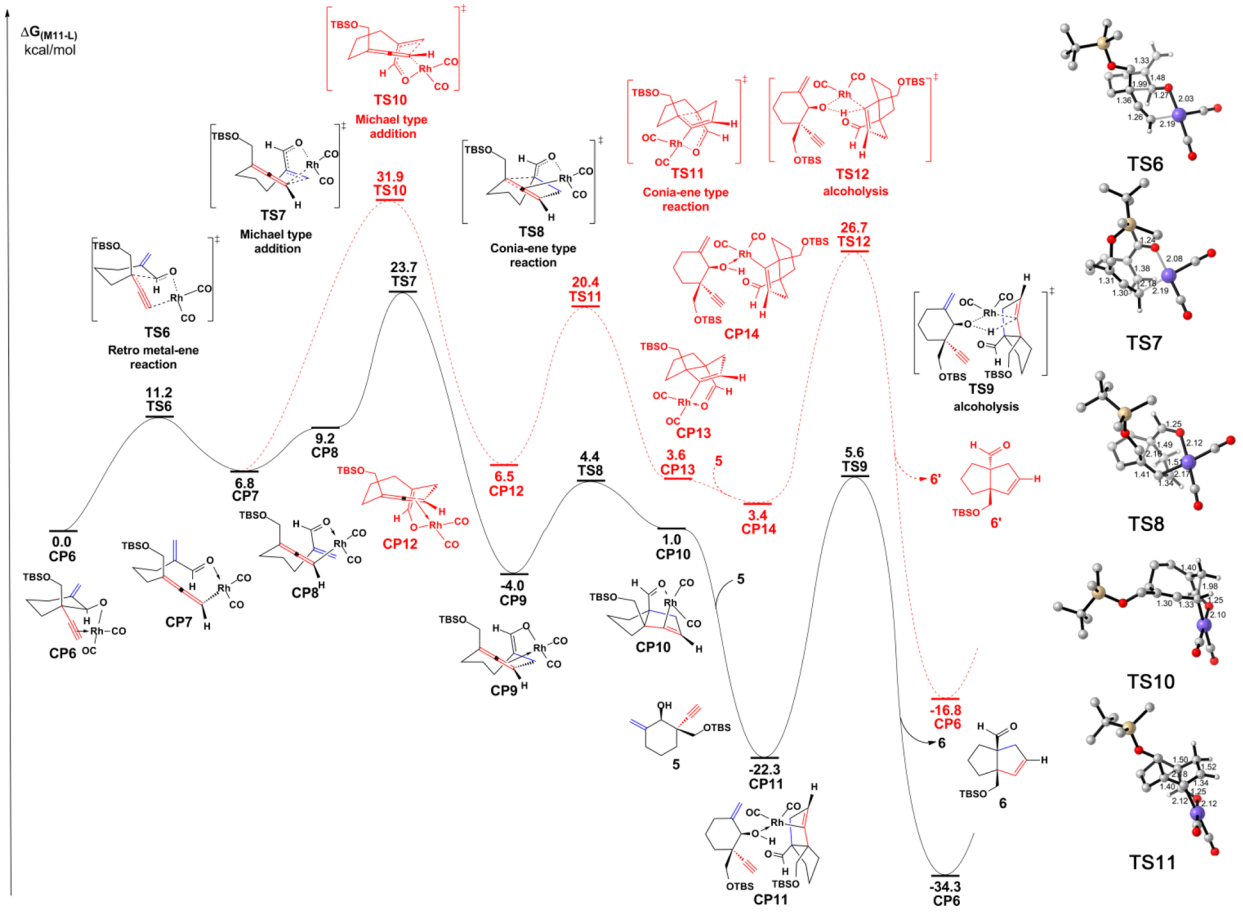

Figure 2. Free-energy profiles and structural information for rhodium-catalyzed synthesis of bicyclo[3.3.0]octane **6**. The values of bond lengths are given by angstrom.

intermediate **CP10**. A Conia-ene-type reaction via transition state **TS8** could then reversibly afford the *cis* bicyclic intermediate **CP10**, with a free energy barrier of only 8.4 kcal/mol. Coordination of another molecule **5** results in irreversible formation of **CP11**, with free-energy release of 23.3 kcal/mol. The demetalation of complex **CP11** could take place via a four-membered-ring transition state **TS9**. After release of the *cis* product **6**, the active intermediate **CP6** would be regenerated irreversibly to finish the catalytic cycle.

In a competing pathway (Figure 2, red lines), an alternative insertion could proceed via transition state **TS10** from intermediate **CP7** to form the *trans* 10-membered-ring intermediate **CP12**.

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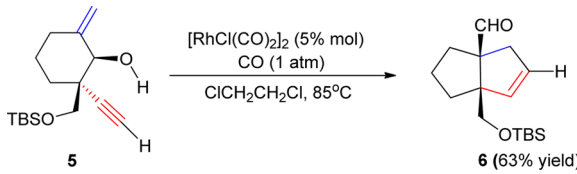
This Michael type addition process determines the orientation of aldehyde group, thereby it determines the stereochemistry of the product. The corresponding *trans* product **6′** could then be generated by subsequent olefin insertion and protonolysis steps. **TS10** is 8.2 kcal/mol energetically less favorable than **TS7**, therefore when **5** (diastereoisomer of **3**) is used as the substrate, only the *cis* product **6** (enantiomer of **4**) could be formed.

To confirm our theoretical prediction, racemic *erythro*-enynol **5**, a diastereoisomer of *threo*-enynol **3**, was used for this reaction. As shown in Scheme 4, racemic *cis*-product **6** was obtained in

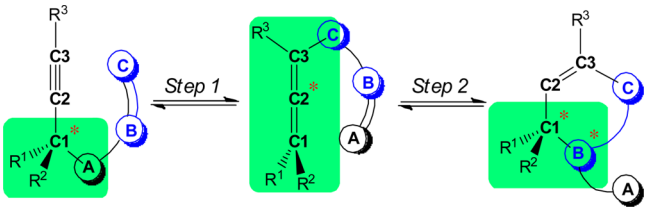
Scheme 4. Intramolecular [3+2] Reaction of in situ Generated Allenyl−Rhodium and Enol Using (1*R*,2*S*)-Enynol 5



63% yield under identical reaction conditions. This result is consistent with our theoretical calculation.

In order to describe the chirality transfer process during this [3+2] cycloaddition reaction, a diagrammatic depiction is abstracted out and shown in Scheme 5. In the first step, when

Scheme 5. Chirality Transfer of Alkyne with α-Chiral Carbon and Allene



the intramolecular reaction between C3 and group **C** takes place, C1−**A** bond would break with concomitant formation of C3−**C** bond, and the chiral center is transferred to the C1−C3 axis from C1 position. Subsequent cyclization reaction of C1 with group **B** leads to the construction of C1−**B** bond. The chiral center thereby returns to C1 position. Meanwhile, the cyclization also breaks the unsaturated bond between group **B** and **A**, thus generating another chiral center in group **B**. This step contains a known axial-to-central chirality transfer process, which is in accordance with proposed concepts of reactivity.[17] As the chirality of all the intermediates is maintained during this course, the stereoselectivity of the product in this type of reaction would be controlled by the stereochemistry of the C1 position in reactant to a certain extent.

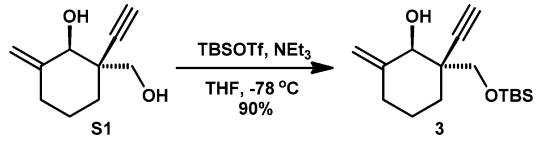
CONCLUSION

In summary, DFT method M11-L was employed to explore the mechanism of this intramolecular [3+2] cycloaddition reaction, which gives [3.3.0] bicyclic ring systems bearing two vicinal quaternary carbon centers at the bridgehead positions. The catalytic cycle involves two possible pathways. One pathway underwent an intramolecular 3,3-sigmatropic migration to form an enolate-rhodium intermediate, a Conia-ene-type reaction of an enolate with an allene, and protonolysis. In another pathway, the enolate-rhodium intermediate would be generated in two steps, a retro propargylation reaction to form an alleno−rhodium intermediate and a Michael-type addition to an enal. The selection of the reaction pathway was determined by the *erythro*/*threo*-stereochemistry of the starting materials. The product stereoselectivity is determined by the α-carbon of alkyne, where a chirality transfer takes place. Only *cis* [3.3.0] bicyclic product was generated, regardless of whether *erythro* or *threo* substrates were used. The theoretical results were consistent with the experimental observations. Future experimental and theoretical studies for the synthesis of [4.3.0] and [5.3.0] bicyclic precursors are underway.

EXPERIMENTAL SECTION

General Experimental Information. In this work, all the reactions were carried out in anhydrous solvents under an argon atmosphere. All the reagents and starting materials were purchased from commercial sources. Based on standard techniques, the flash chromatography was achieved using 200−300 mesh silica gel with the indicated solvent system. The solvents employed for chromatography in this work were technical grade and distilled before use. The developed chromatograms were visualized by UV absorbance (254 nm). Analytical thin-layer chromatography (TLC) was carried out on precoated, glass-backed silica gel plates. The ^{1}H and ^{13}C NMR data were recorded on 400 MHz NMR and 500 MHz NMR spectrometers. The abbreviations given below were employed to clarify the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. The ion mass/charge (m/z) ratios, given in atomic mass units, are gained by HRMS (ESI) analysis with a quadrupole time-of-flight mass spectrometer. IR spectra were measured as dry fimas (KBr), and peaks were shown by means of wavenumber (cm^{-1}).

Synthesis of Compound ***3***. To a solution of chiral diol **S1**[6a] (20 mg, 0.12 mmol) and Et_3N (24 mg, 0.24 mmol) in dry THF (3 mL) was



added TBSOTf (33 mg, 0.12 mmol) at −78 °C in a dropwise manner. Subsequently, the reaction mixture was stirred at the same temperature for 15 min, and quenched with water (2 mL). Ether (3 × 3 mL) is then employed for the extraction of aqueous layer. Finally, the combined organic layers were washed using brine (2 mL), and dried over Na_2SO_4. The solvent was removed under vacuum condition. The silylether **3** (30 mg, 90%) was obtained as a colorless liquid through the purification of the residue using a flash chromatography on silica gel (hexane/ethyl acetate =30/1); R_f = 0.42 (silica gel, EtOAc/hexanes =1/20); $[\alpha]^{25}_{D}$ = +2.78 (c = 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.06 (d, J = 1.5, 1H), 4.99−4.82 (m, 1H), 4.11 (d, J = 7.4, 1H), 3.91 (d, J = 9.5, 1H), 3.60 (d, J = 9.5, 1H), 2.68 (d, J = 7.5, 1H), 2.47−2.29 (m, 1H), 2.19 (s, 1H), 1.96 (dd, J = 15.9, 8.6, 1H), 1.75−1.63 (m, 4H), 0.92 (s, 9H), 0.10 (d, J = 3.5, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 147.9, 107.2, 83.7, 73.6, 73.4, 68.6, 47.6, 34.0, 32.5, 25.9, 23.3, 18.3, −5.5, −5.5; IR (film, cm^{-1}): 3309, 2935, 2885, 2858, 1257, 1168, 1080; HRMS (ESI) calcd for $C_{16}H_{29}O_2Si$ [M+H$^+$]: 281.1931, found: 281.1933.

Synthesis of Compound ***5***. To a solution of diol **S2** (18 mg, 0.11 mmol) and Et_3N (22 mg, 0.22 mmol) in dry THF (3 mL) was added TBSOTf (29 mg, 0.11 mmol) at −78 °C in a dropwise manner. Subsequently, the reaction mixture was stirred at the same temperature for 15 min, and quenched with water (1 mL). Ether (3 × 3 mL) is then employed for the extraction of aqueous layer. Finally, the combined organic layers were washed using brine (2 mL), and dried over Na_2SO_4. The solvent was removed under vacuum condition. The silylether **5** (26 mg, 84%) was obtained as a colorless liquid through

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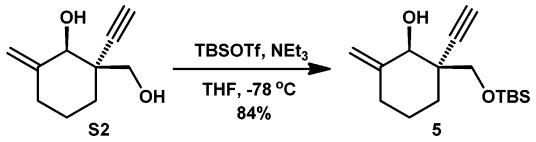
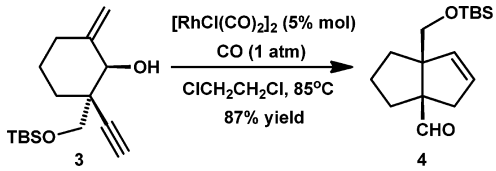


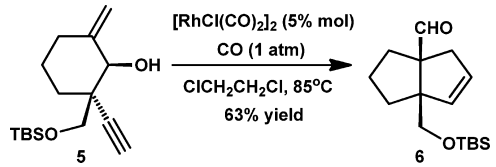
the purification of the residue using a flash chromatography on silica gel (hexane/ethyl acetate =30/1); R_f = 0.44 (silica gel, EtOAc/hexanes =1/20); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.97 (s, 1H), 4.88 (s, 1H), 4.26 (d, J = 2.5, 1H), 4.02−3.64 (m, 3H), 2.48−2.24 (m, 1H), 2.16 (s, 1H), 2.12−1.95 (m, 2H), 1.79−1.52 (m, 2H), 1.52−1.36 (m, 1H), 0.91 (s, 9H), 0.10 (d, J = 4.6, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 146.8, 110.7, 86.1, 78.4, 71.9, 69.1, 43.4, 30.4, 29.0, 25.8, 23.1, 18.2, −5.6, −5.6; IR (film, cm^{-1}): 3324, 2920, 2896, 2837, 1230, 1103, 1081; HRMS (ESI) calcd for $C_{16}H_{29}O_2Si$ [M+H$^+$]: 281.1931, found:281.1930.

Synthesis of Chiral Compound 4. To a solution of enynol **3** (28 mg, 0.10 mmol) in $ClCH_2CH_2Cl$ (4 mL) was added $[RhCl(CO)_2]_2$



(1.9 mg). The product **4** (24 mg) is obtained in 87% yield by stirring the mixture under balloon pressure of CO at 85 °C for 4 h. The solvent was then removed under vacuum condition after being cooled down to room temperature. Subsequent purification process was performed through a flash chromatography on silica gel (Hexane/EtOAc = 20/1); $[\alpha]^{25}_D$ = +55 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.72 (s, 1H), 5.78−5.56 (m, 1H), 5.29−5.01 (m, 1H), 3.67−3.40 (m, 2H), 3.24−2.99 (m, 1H), 2.22−2.04 (m, 2H), 1.79−1.71 (m, 1H), 1.70−1.59 (m, 2H), 1.55−1.45 (m, 2H), 0.86 (s, 9H), 0.01 (d, J = 2.9, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.1, 134.6, 129.8, 70.5, 65.2, 63.2, 42.5, 37.3, 34.7, 25.8, 24.7, 18.2, −5.5, −5.6; IR (film, cm^{-1}): 2954, 2924, 1720, 1261, 1085; HRMS (ESI) calcd for $C_{16}H_{29}O_2Si$ [M+H$^+$]: 281.1931, found: 281.1935.

Synthesis of Compound 6. To a solution of enynol **5** (20 mg, 0.07 mmol) in $ClCH_2CH_2Cl$ (2.8 mL) was added $[RhCl(CO)_2]_2$ (1.3 mg).



The product **6** (12.6 mg) is obtained in 63% yield by stirring the mixture under balloon pressure of CO at 85 °C for 4 h. The solvent was then removed under vacuum condition after being cooled down to room temperature. Subsequent purification process was performed through a flash chromatography on silica gel (Hexane/EtOAc = 20/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 5.75−5.65 (m, 1H), 5.25−5.12 (m, 1H), 3.53 (t, J = 5.9, 2H), 3.16−3.04 (m, 1H), 2.21−2.07 (m, 2H), 1.80−1.62 (m, 3H), 1.54−1.46 (m, 2H), 0.85 (s, 9H), −0.00 (d, J = 2.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.1, 134.5, 129.8, 70.5, 65.1, 63.1, 42.4, 37.3, 34.7, 25.8, 24.7, 18.1, −5.6, −5.7; IR (film, cm^{-1}): 2975, 2890, 1744, 1301, 1165; HRMS (ESI) calcd for $C_{16}H_{29}O_2Si$ [M+H$^+$]: 281.1931, found: 281.1933.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01429.

Cartesian coordinates, energies of all reported structures, full authorship of Gaussian 09, and the NMR spectra (PDF)

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Author Contributions

⊥X.Q. and S.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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