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A Concise Total Synthesis of (−)-Mesembrine

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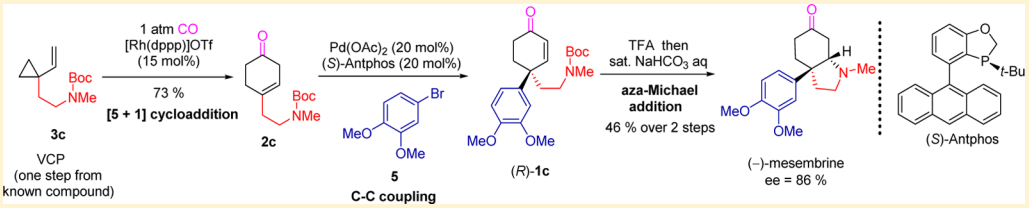
Supporting Information



ABSTRACT: A concise total synthesis of mesembrine (four steps from known compound) was achieved both racemically and asymmetrically. Two key reactions were used here. One is the Rh(I)-catalyzed [5 + 1] cycloaddition of vinylcyclopropane **3c** and CO. The other one is Buchwald's Pd-catalyzed coupling reaction that coupled β,γ-cyclohexenone **2c** with aryl bromide **5** (using dppe ligand for racemic or (*S*)-Antphos ligand for asymmetric synthesis) to give γ,γ-disubstituted α,β-cyclohexenone **1c**. Finally, aza-Michael addition converted **1c** to mesembrine.

(−)-Mesembrine, a natural product extracted from a South African plant *Sceletium Tortuosum* (Figure 1),[1] has shown excellent promise as an antianxiety and antiaddiction treatment.[2] This molecule is a member of the benzylphenethylamine-type alkaloid family[3] and contains a synthetically challenging bridgehead quaternary carbon with one aryl substituent (Figure 1). Since its discovery in 1957, this molecule has been an intensely pursued target for total synthesis. To date, more than 40 routes toward its total and formal syntheses have been reported.[4] Despite these advances, the appealing structure with the challenging bridgehead quaternary carbon and significant biological activity of mesembrine have been stimulating chemists to design a new strategy to synthesize this molecule and its analogues under the consideration of step economy.[5]

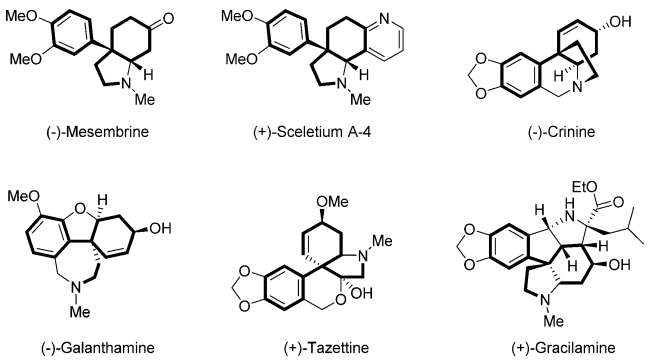


Figure 1. (−)-Mesembrine and representative benzylphenethylamine-type alkaloids.

We report here our concise synthesis of mesembrine, both racemic and asymmetric. Our approach to the total synthesis of mesembrine was inspired by both Buchwald's work and our own [5 + 1] reaction (Scheme 1). In 2008, Hyde and Buchwald developed a palladium-catalyzed cross-coupling reaction of β,γ-cyclohexenones with aryl bromides to γ,γ-disubstituted α,β-cyclohexenones.[6] One salient feature of this reaction is that a quaternary carbon can be built. The authors also demonstrated that its asymmetric version can be realized by using the chiral phosphine ligand (*R*)-DTBM-Segphos.[6] Furthermore, the Buchwald group tandemed this coupling reaction with aza-Michael addition of amine to build an indoline skeleton when *o*-bromoaniline was used as the coupling partner.

The starting material, β,γ-cyclohexenones in Buchwald's chemistry, was prepared by Birch reduction of aryl compounds.[7] Recently, we developed a Rh(I)-catalyzed [5 + 1] cycloaddition of vinylcyclopropanes (VCPs) and CO (Scheme 1).[8a] The [5 + 1] cycloaddition can be used to construct either β,γ-cyclohexenones or α,β-cyclohexenones, depending on whether DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was used or not in the reaction. Considering that our [5 + 1] reaction has broad scope, preparation of VCPs are easy, and the reaction conditions are mild, we envisioned that a combination of our [5 + 1] reaction for the synthesis of β,γ-cyclohexenones, with Buchwald's coupling chemistry, may provide an efficient route to γ,γ-disubstituted α,β-cyclohexenones in both racemic and asymmetric fashions.

The total synthesis of mesembrine provides a chance to show the power of this combination for the synthesis of γ,γ-disubstituted α,β-cyclohexenones. Scheme 2 shows the retrosynthetic analysis of mesembrine. We proposed that the

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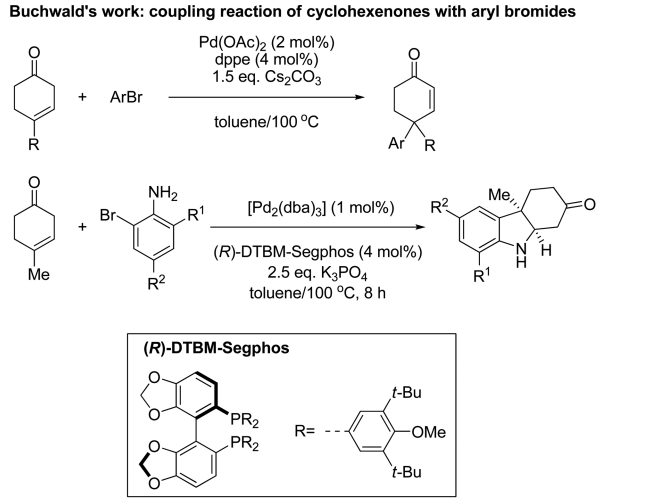
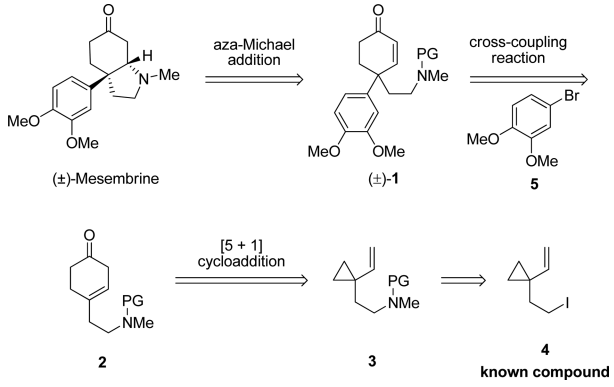
Scheme 1. Pd(0)-Catalyzed Coupling Reaction and Rh(I)-Catalyzed [5 + 1] Cycloaddition



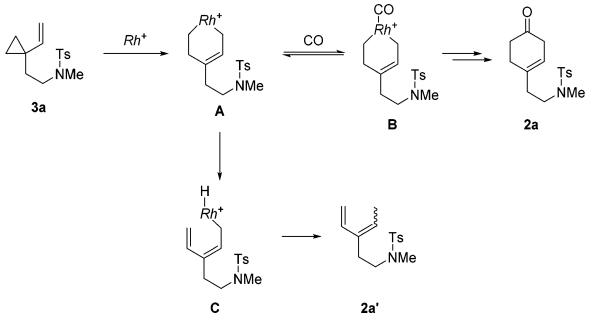
Scheme 2. Synthetic Strategy for (±)-Mesembrine



pyrrolidine skeleton could be synthesized by an intramolecular aza-Michael addition from *N*-protected *γ*,*γ*-disubstituted *α*,*β*-cyclohexenone **1**.[9] The cyclohexenone **1** could be accessed by Buchwald coupling reaction using *β*,*γ*-cyclohexenone **2** and aryl bromide **5**. The cyclohexenone **2** could be prepared by our Rh(I)-catalyzed [5 + 1] cycloaddition of the corresponding VCP **3** with CO. VCP **3** was expected to be synthesized from the known compound **4**[10] with a protected methylamine via a S_N2 reaction. This strategy could also be advanced to its asymmetric version if Buchwald's chiral DTBM-Segphos ligand or other chiral ligands was used.

Because the Ts group (tosyl) is stable under both acidic and basic conditions and it often acts as a good protecting group on nitrogen atom,[11] we first synthesized Ts-VCP **3a** as the substrate to test whether the [5 + 1] cycloaddition, coupling reaction, and the deprotection reaction can all work (Scheme 3). The known compound **4** reacted with TsNHMe to give the corresponding **3a** in 80% yield. We then attempted the key Rh-catalyzed [5 + 1] cycloaddition of **3a** with CO by using the previous reported reaction conditions.[8a] Fortunately, under a balloon-pressured mixed gas of CO and N_2 (the ratio of CO/N_2 is 1/4 and this is usually labeled as 0.2 atm CO), using 10 mol % Rh(dppp)OTf, we obtained the target molecule **2a** in 43% yield. When the loading of catalyst was increased to 15 mol %, the yield of **2a** was improved to 52%. The low yield of this [5 + 1] reaction is due to the presence of a side reaction: side product **2a′**, which was generated from the *β*-H elimination of six-membered rhodacycle intermediate **A** (Scheme 4), was obtained in 37% yield.[12] We speculated that

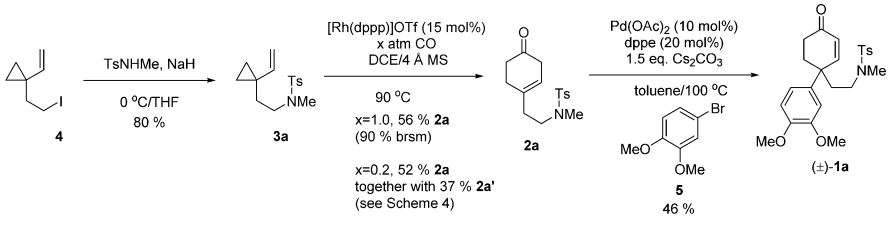
Scheme 4. Proposed Mechanisms for the [5 + 1] Reaction and the Formation of *β*-H Elimination Product



increasing the pressure of CO and its concentration in the reaction system could inhibit the *β*-H elimination reaction and, consequently, improve the yield of [5 + 1] reaction. To our delight, under balloon pressure of CO atmosphere (1 atm), we obtained the [5 + 1] cycloadduct **2a** in 56% isolated yield, together with the remaining starting material (Scheme 3). No side product **2a′** was observed. The [5 + 1] reaction yield in this case was 90% based on recovered starting material (brsm).

Then we tested the coupling reaction of cyclohexenone **2a** with 4-bromoveratrole **5** under the reaction conditions reported by the Buchwald group.[6] When we used 2 mol % of $Pd(OAc)_2$, 4 mol % of 1,2-bis(diphenylphosphino)ethane (dppe), 1.0 equiv of compound **2a**, 1.1 equiv of 4-bromoveratrole, and 1.5 equiv of Cs_2CO_3 (heating in toluene at 100 °C), to our

Scheme 3. Synthesis of Ts-Protected Cyclohexenone 1a



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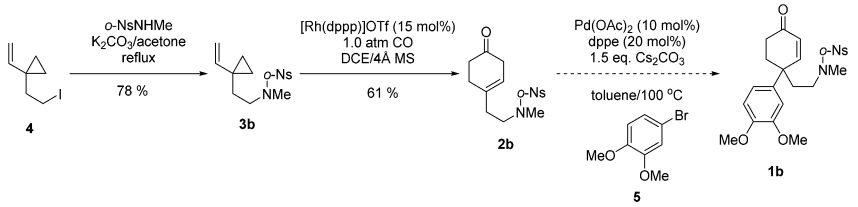
Scheme 5. Synthesis of Cyclohexenone 2b



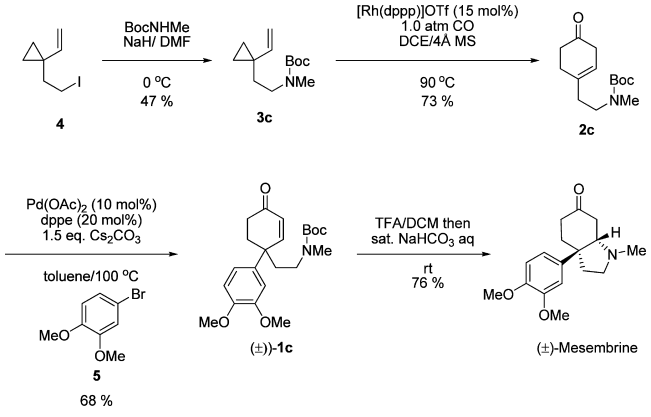
disappointment, we got a complex mixture. Considering that some side reactions (such as dehydrogenation) may occur if the aryl bromide was used in excess,[13] we reduced the amount of **5** from 1.1 to 0.8 equiv. Unfortunately, a complex mixture was still observed. Finally, we were pleased to find that when the loadings of both pre-catalyst and ligand were increased (10 mol % of $Pd(OAc)_2$ and 20 mol % of dppe), the target coupling reaction proceeded smoothly and the desired compound (±)-**1a** was obtained in 46% yield (Scheme 3).

With compound (±)-**1a** in hand, we tried to remove the tosyl group to achieve an intramolecular aza-Michael addition to accomplish the total synthesis of (±)-mesembrine. We attempted several conditions such as using TMSI,[14] Mg/MeOH,[15] and Na/naphthalene[16] to complete the synthesis. Only Na/naphthalene could provide the target product (±)-mesembrine in a low yield. We did not try other conditions to remove the Ts group. Instead, we planned to use other protecting groups to accomplish the total synthesis of mesembrine.

Considering that the *o*-Ns group (*o*-nitrobenzenesulfonyl) is also a sulfamide-type protecting group and it can be easily removed with thiols,[11] we prepared *o*-Ns-VCP **3b**. The yield of [5 + 1] cycloaddition was 61%. Under optimized conditions, however, the coupling reaction did not work, giving a complex mixture (Scheme 5). The reason for this is not known at this time.

Because the Boc group (*tert*-butoxycarbonyl) is stable under basic ambient conditions and easy to remove under acidic ambient conditions,[11] we tried to synthesize Boc-VCP **3c** to accomplish the synthesis of mesembrine (Scheme 6). Compound **4** was reacted with BocNHMe, giving Boc-VCP **3c** in 47% yield. Under the optimized conditions of [5 + 1] cycloaddition, target cyclohexenone **2c** was obtained in 73% isolated yield. Using a higher pressure of CO did not improve the reaction yield of the [5 + 1] reaction (when the pressure of CO was increased to 5 atm, the yield of [5 + 1] reaction was only 52−56%). Then, 0.7 equiv of **5** was used to carry out the coupling reaction with 1.0 equiv of **2c**, and we found that (±)-**1c** was obtained in 68% yield in this case (we want to mention that, in all of the coupling reactions, excess **2** could not be recovered). After removal of the Boc group using TFA, the final product (±)-mesembrine was obtained in 76% yield. ^{1}H NMR, ^{13}C NMR, IR, and HRMS data of the synthesized mesembrine are in agreement with those reported in the literature.[4h]

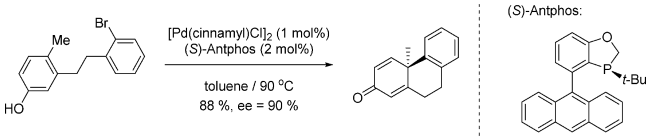
Scheme 6. Concise Total Synthesis of (±)-Mesembrine



We then tried to use chiral phosphine ligands to test the asymmetric coupling reaction so that an asymmetric total synthesis of mesembrine could be realized. First, we used chiral ligand (*S*)-DTBM-Segphos, which was used by Hyde and Buchwald,[6] to do the coupling reaction. Fortunately, the expected reaction occurred and gave product **1c** in 40% yield. Removing Boc group in **1c** gave the product mesembrine, which was found to be racemic as determined by chiral HPLC.

We noticed that Tang and co-workers developed several chiral monophosphine ligands that can facilitate the Pd-catalyzed coupling reaction to form congested C−C bonds,[17] including the dearomatization of bromine-substituted phenol (Scheme 7).[17b,c] We envisioned that this reaction occurs via a mechanism similar to that of the Buchwald reaction in Scheme 1 and could be a choice for our asymmetric synthesis. Therefore, we tested the Pd-catalyzed coupling reaction using Tang's (*S*)-Antphos ligand.[17b,c] Using 10 mol % of $Pd(OAc)_2$ and 10 mol % of (*S*)-Antphos, the target compound (*R*)-**1c** was obtained in 30% yield (0.7 equiv of **5**, 1 equiv of **2c** were used). After removal of the Boc group, we obtained the product (−)-mesembrine in 73% yield and 86% ee. We then increased the loading of catalyst to 20 mol % and decreased the amount of aryl bromide to 0.5 equiv (**2c** was 1 equiv), and the yield of coupling reaction was 63% (Scheme 8). Removal of the Boc group from (*R*)-**1c** gave the (−)-mesembrine in 73% yield with 86% ee.

Scheme 7. Asymmetric Intramolecular Phenol/Aryl Bromide Coupling Reaction by Tang



In summary, we have accomplished both racemic and asymmetric total syntheses of mesembrine, each in four steps from known compounds via Rh(I)-catalyzed [5 + 1] cycloaddition of VCP with CO, and the Pd(0)-catalyzed coupling reaction of β,γ-cyclohexenone with aryl bromide. This strategy could be used to synthesize other benzylphenethylamine-type alkaloids with a quaternary bridgehead carbon center. Further application of this strategy in synthesis is ongoing in our laboratory.

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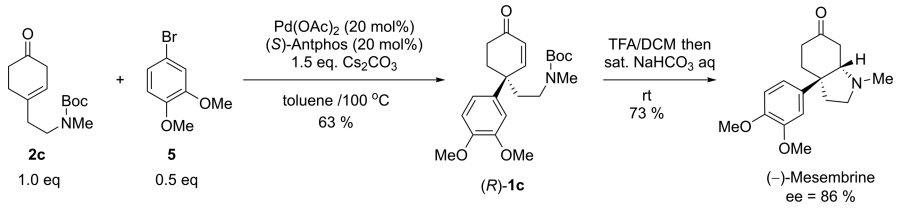
Scheme 8. Total Synthesis of (−)-Mesembrine



EXPERIMENTAL SECTION

General Information. Air- and moisture-sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry argon or nitrogen. Similarly, sensitive liquids and solutions were transferred via syringe. Reactions were stirred using Teflon-coated magnetic stir bars. Elevated temperatures were maintained using thermostat-controlled silicone oil baths. Organic solutions were concentrated using a rotary evaporator with a desktop vacuum pump. Tetrahydrofuran and toluene were distilled from sodium and benzophenone prior to use. Dichloromethane (DCM) was distilled from CaH_2 prior to use. *N,N*-Dimethylformamide and methanol were dried by molecular sieves prior to use. Dichloroethane (DCE) was superdry level. Synthetic reagents were purchased and used without further purification unless otherwise indicated. Analytical TLC was performed with 0.25 mm silica gel G plates. The TLC plates were visualized by ultraviolet light and treatment with phosphomolybdic acid stain followed by gentle heating. Purification of products was accomplished by flash chromatography on silica gel, and the purified compounds showed a single spot by analytical TLC. The diastereomeric ratio was determined by ^{1}H NMR of crude reaction mixtures. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C using TMS (^{1}H, 0.00 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm) as internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration. IR spectra were recorded on Fourier transform infrared spectrometer and reported in wavenumbers (cm^{-1}). HRMS were recorded on an FTMS mass spectrometer (ESI). Optical rotations were measured on a spectrometer. Enantiomeric excess (ee) values were determined by analytical liquid chromatography (HPLC) analysis on a chromatograph (Daicel chiral columns Chiralpak AS-H (4.6 × 250 mm)). PE refers to petroleum ether, and EA refers to ethyl acetate.

*N,4-Dimethyl-N-(2-(1-vinylcyclopropyl)ethyl)-benzenesulfonamide (**3a**).* To NaH (167 mg, 60% in mineral oil, 4.18 mmol) was added solution of TsNHMe (709.9 mg, 3.83 mmol in 15 mL of THF) at 0 °C. After the solution was stirred at room temperature for 5 min, a solution of **4**[9] (773.9 mg, 3.48 mmol) in DMF (5 mL) was added. Then the reaction solution was stirred for anothor 15 h and quenched with dropwise addition of water. The aqueous mixture was extracted with diethyl ether. The combined organic phase was dried with anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 2:1) afforded product **2a** as a colorless oil (80.4 mg, 52% yield) and **2a′** as a colorless oil mixture of *Z*/*E* isomers (51.3 mg, 37% yield). 5.51 ppm is assigned for *Z* isomer (methyl and vinyl is in *cis* configuration) while 5.64 is assigned to *E* isomer, and the *Z*/*E* is about 7/1, based on analog to similar compounds.[18]

3a. Colorless oil. TLC R_f (PE/EA 5:1) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.55−0.63 (m, 4H), 1.65−1.72 (m, 2H), 2.43 (s, 3H), 2.74 (s, 3H), 3.04−3.11 (m, 2H), 4.92 (dd, J = 10.6, 0.8 Hz, 1H), 4.94 (dd, J = 17.6, 0.8 Hz, 1H), 5.49 (dd, J = 17.6, 10.6 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H) 7.66 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 142.7, 134.8, 129.6, 127.3, 111.3, 48.4, 35.2, 34.4, 21.5, 20.3, 14.0. IR (neat): ν 3081, 2998, 2927, 2866, 1638, 1598, 1460, 1341, 1161, 1090, 970, 816 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{22}NO_2S^+$ ($M + H^+$) 280.1366, found 280.1358.

*N,4-Dimethyl-N-(2-(4-oxocyclohex-1-en-1-yl)ethyl)-benzenesulfonamide (**2a**).* A solution of $[Rh(CO)_2Cl]_2$ (27.8 mg, 0.072 mmol) and AgOTf (37.0 mg, 0.144 mmol) in anhydrous DCE (9.5 mL) was stirred for 15 min at room temperature. After precipitation for 5 min, the supernatant (4.5 mL, the used $Rh(CO)_2OTf$ was estimated as 0.068 mmol) was added from the above solution to a reaction tube with dppp (28.0 mg, 0.068 mmol) and 4 Å MS (300 mg). After 5 min of stirring, a solution of substrate **3a** (127.2 mg, 0.46 mmol) in DCE (4.5 mL) was added to the tube. The reaction solution was degassed by bubbling 1.0 atm CO for 5 min. The reaction mixture was placed in a 90 °C oil bath and stirred under the balloon pressure gas of CO for 22 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 2:1) afforded the starting material **3a** (50.6 mg) and product **2a** as a colorless oil (77.7 mg, 56% yield, 90% brsm).

2a. Colorless oil. TLC R_f (PE/EA 5:1) = 0.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (t, J = 7.1 Hz, 2H), 2.43 (s, 3H), 2.42−2.47 (m, 2H), 2.49−2.54 (m, 2H) 2.73 (s, 3H), 2.84−2.88 (m, 2H), 3.13 (t, J = 7.1 Hz, 2H), 5.52 (m, 1H), 7.32 (d, J = 8.0, 2H), 7.67 (d, J = 8.0, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.3, 143.4, 135.2, 134.6, 129.7, 127.3, 120.6, 48.4, 39.6, 38.5, 35.2, 34.6, 28.2, 21.5. IR (neat): ν 2959, 2925, 2872, 2361, 2342, 1713, 1686, 1598, 1459, 1338, 1160, 1090, 817, 721 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{22}NO_3S^+$ ($M + H^+$) 308.1315, found 308.1308.

*N-Methyl-N-(tosylmethyl)-3-vinylpent-3-en-1-amine (**2a′**).* A solution of $[Rh(CO)_2Cl]_2$ (27.8 mg, 0.072 mmol) and AgOTf (37.0 mg, 0.144 mmol) in anhydrous DCE (9.5 mL) was stirred for 15 min at room temperature. After precipitation for 5 min, supernatant (5.0 mL, the used $Rh(CO)_2OTf$ was estimated to be 0.076 mmol) was added from the above solution to a reaction tube with dppp (31.0 mg, 0.075 mmol) and 4 Å MS (330 mg). After 5 min of stirring, a solution of substrate **3a** (139.5 mg, 0.50 mmol) in DCE (5.0 mL) was added to the tube. Then the reaction solution was degassed by bubbling 0.2 atm CO (this is a mixed gas of N_2 and CO with ratio of 4:1) for 5 min. The reaction mixture was placed in a 90 °C oil bath and stirred under 0.2 atm of CO for 22 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 2:1) afforded product **2a** as a colorless oil (80.4 mg, 52% yield) and **2a′** as a colorless oil mixture of *Z*/*E* isomers (51.3 mg, 37% yield). 5.51 ppm peak of ^{1}H NMR of **2a′** is assigned for *Z* isomer (the methyl and vinyl groups are in a cis configuration) while 5.64 ppm peak is assigned for *E* isomer, and the *Z*/*E* ratio is about 7/1. The relative stereochemistry of *Z* and *E* is derived from comparison of their NMR spectra with those of similar compounds.[18]

2a′. Colorless oil. TLC R_f (PE/EA 5:1) = 0.48. Major isomer (Z-**2a′**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (d, J = 6.8 Hz, 3H), 2.40−2.47 (m, 5H), 2.77 (s, 3H), 3.05−3.11 (m, 2H), 5.11 (d, J = 11.2 Hz, 1H), 5.24 (d, J = 17.6 Hz, 1H), 5.51 (qm, J = 7.0 Hz, 1H), 6.64 (dd, 17.6, 11.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 135.0, 133.8, 131.9, 129.6, 127.3, 127.1, 113.4, 50.0, 35.1, 32.5, 21.5, 13.2. Selected peaks of minor isomer (*E*-**2a′**) of ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (d, J = 7.6 Hz,0.45 H), 2.82 (s, 0.45H), 2.98−3.04 (m, 0.3H), 4.93 (d, J = 11.2 Hz, 0.15H), 5.64 (q, J = 7.0 Hz, 0.15H), 6.25 (dd, J = 17.6, 10.8 Hz, 0.15H). IR (neat): ν 3016, 2925, 2865, 1598, 1459, 1340, 1305, 1161, 1459, 1090, 944, 816 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{22}NO_2S^+$ ($M + H^+$) 280.1366, found 280.1358.

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*(±)-N-(2-(3′,4′-Dimethoxy-4-oxo-3,4-dihydro[1,1′-biphenyl]-1(2H)-yl)ethyl)-N,4-dimethylbenzenesulfonamide [(±)-**1a**].* A suspension of $Pd(OAc)_2$ (2.5 mg, 0.011 mmol), dppe (8.8 mg, 0.022 mmol), and Cs_2CO_3 (53.7 mg, 0.16 mmol) in toluene (1.0 mL) was stirred in a 100 °C oil bath for 10 min. Then a solution of **5** (19.2 mg. 0.089 mmol) and **2a** (33.1 mg, 0.11 mmol) in toluene (1.3 mL) was added. The reaction mixture was heated at 100 °C for 4 h. Then the reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 2:1) afforded product (±)-**1a** as a yellow oil (18.0 mg, 46% yield, calculated based on the amount of **5**). This reaction gave also some unidentified side products, judged from TLC.

(±)-**1a**. Yellow oil. TLC R_f (PE/EA 1:1) = 0.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06−2.16 (m, 1H), 2.17−2.24(m, 3H), 2.24−2.37 (m, 2H), 2.41 (s, 3H), 2.70 (s, 3H), 2.83−3.00 (m, 2H), 3.88 (s, 3H), 3.90 (s,3H), 6.18 (d, J = 10.2 Hz, 1H), 6.77−6.81 (m, 1H), 6.82−6.85 (m, 2H), 7.05 (d, J = 10.2 Hz, 1H), 7.27 (d, J = 7.4 Hz, 2H), 7.56 (d, J = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 153.9, 149.3, 148.1, 143.4, 134.6, 134.5, 129.8, 129.7, 127.3, 119.1, 111.1, 109.8, 56.0, 55.9, 46.5, 42.7, 39.4, 36.5, 35.3, 34.4, 21.4. IR (neat): ν 2954, 2931, 2871, 2861, 1685, 1678, 1518, 1460, 1339, 1257, 1160, 1026, 815, 807 cm^{-1}. HRMS (ESI): calcd for $C_{24}H_{30}NO_5S^+$ (M + H$^+$) 444.1839, found 444.1846.

*N-Methyl-2-nitro-N-(2-(1-vinylcyclopropyl)ethyl)-benzenesulfonamide (**3b**).* A suspension of **4** (234.9.1 mg, 1.06 mmol), *o*-NsNHMe (457.0 mg, 2.11 mmol), and K_2CO_3 (586 mg, 4.24 mmol) in anhydrous acetone (10.0 mL) was heated in a 60 °C oil bath for 12 h and quenched with water. The aqueous mixture was extracted with diethyl ether. The combined organic phase was dried with anhyous sodium sulfate and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA) afforded the product **3b** as a yellow oil (256.8 mg, 78% yield).

3b. Yellow oil. TLC R_f (PE/EA 2:1) = 0.53. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.57−0.64 (m, 4H), 1.71−1.77 (m, 2H), 2.92 (s, 3H), 3.28−3.33 (m, 2H), 4.94 (dd, J = 10.8, 0.8 Hz, 1H), 4.96 (dd, J = 17.3, 0.8 Hz, 1H), 5.48 (dd, J = 17.3, 10.8 Hz, 1H), 7.59−7.64 (m, 1H), 7.66−7.73 (m, 2H), 7.94−7.99 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 142.5, 133.4, 132.5, 131.5, 130.6, 124.0, 111.4, 48.2, 34.8, 34.2, 20.2, 14.0. IR (neat): ν 3584, 3083, 2932, 1635, 1544, 1461, 1348, 1163, 1058, 974, 774, 695, 580 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{19}N_2O_4S^+$ (M + H$^+$) 311.1060, found 311.1062.

*N-Methyl-2-nitro-N-(2-(4-oxocyclohex-1-en-1-yl)ethyl)-benzenesulfonamide (**2b**).* A solution of $[Rh(CO)_2Cl]_2$ (2.8 mg, 0.0072 mmol) and AgOTf (4.5 mg, 0.0175 mmol) in anhydrous DCE (1.5 mL) was stirred for 15 min at room temperature. After precipitation for 5 min, the supernatant was added to a reaction tube with dppp (6.0 mg, 0.0145 mmol) and 4 Å MS (65 mg). After 5 min of stirring, a solution of substrate **3b** (30.2 mg, 0.0973 mmol) in DCE (1.5 mL) was added to the tube. Then the reaction solution was degassed by bubbling 1.0 atm CO for 5 min. The reaction mixture was moved to a 90 °C oil bath and stirred under the balloon pressure gas of CO for 24 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 3:1) afforded product **2b** as a colorless oil (20.0 mg, 61% yield).

2b. Colorless oil. TLC R_f (PE/EA 2:1) = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (t, J = 7.1 Hz, 2H), 2.42−2.48 (m, 2H), 2.49−2.54 (m, 2H), 2.85−2.88 (m, 2H), 2.90 (s, 3H), 3.38 (t, J = 7.1 Hz, 2H), 5.53−5.57 (m, 1H), 7.60−7.64 (m, 1H), 7.66−7.74 (m, 2H), 7.95−8.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 148.1, 134.8, 133.5, 132.4, 131.5, 130.9, 124.1, 121.1, 48.6, 39.6, 38.4, 35.3, 34.2, 28.2. IR (neat): ν 3584, 2925, 1712, 1544, 1440, 1346, 1267, 1163, 1057, 953 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{19}N_2O_5S^+$ (M + H$^+$) 339.1009, found 339.1017.

*tert-Butyl Methyl (2-(1-Vinylcyclopropyl)ethyl)carbamate (**3c**).* To a suspension of NaH (361 mg, 60% in mineral oil, 9.02 mmol) in anhydrous DMF (7 mL) was added solution of BocNHMe (1.1812 g, 9.00 mmol in 7 mL DMF) at 0 °C. After the suspension was stirred at room temperature for 45 min, a solution of **4** (502.1 mg, 2.26 mmol) in DMF (8.0 mL) was added. Then the reaction solution was stirred for anothor 16 h and quenched by dropwise addition of water. The aqueous mixture was extracted with diethyl ether The combined organic phase was dried with anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 5:1) afforded product **3c** as a colorless oil (239.4 mg, 47% yield).

3c. Colorless oil. TLC R_f (PE/EA 5:1) = 0.70 1H NMR (400 MHz, CDCl3): δ 0.55−0.63 (m, 4H), 1.46 (s, 9H), 1.60−1.65 (m, 2H), 2.84 (s, 3H), 3.24−3.30 (m, 2H), 4.93 (dd, J = 10.6, 1.0 Hz, 1H), 5.00 (d, J = 17.5 Hz, 1H), 5.52 (dd, J = 17.5, 10.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 143.2, 110.9, 79.1, 47.1, 34.4 and 33.9, 33.3, 28.5, 20.3, 14.0. The redundant peaks of 34.4 and 33.9 are due to the rotation of the C−N bond in the molecule. IR (neat): ν 3081, 2976, 2931, 1698, 1637, 1482, 1395, 1212, 1053, 955, 772 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{24}NO_2^+$ (M + H$^+$): 226.1802. Found: 226.1792.

*tert-Butyl Methyl (2-(4-Oxocyclohex-1-en-1-yl)ethyl)carbamate (**2c**).* A solution of $[Rh(CO)_2Cl]_2$ (27.6 mg, 0.071 mmol) and AgOTf (44.0 mg, 0.171 mmol) in anhydrous DCE (9.5 mL) was stirred for 15 min at room temperature. After precipitation for 5 min, the supernatant was added to a reaction tube with dppp (58.8 mg, 0.143 mmol) and 4 Å MS (600 mg). After the solution was stirred for 5 min, a solution of substrate **3c** (213 mg, 0.95 mmol) in DCE (9.5 mL) was added to the tube. Then the reaction solution was degassed by bubbling 1.0 atm CO for 5 min. The reaction mixture was moved in a 90 °C oil bath and stirred under the balloon pressure gas of CO for 24 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 3:1) afforded product **2c** as a colorless oil mixture of amide rotamers (175.8 mg, 73% yield).

2c. Colorless oil. TLC R_f (PE/EA 5:1) = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 8H) and 1.46 (s, 1H), 2.26 (t, J = 7.0 Hz, 2H) 2.44−2.53 (m, 4H), 2.82−2.91 (m, 2H), 2.85 (s, 3H) 3.34 (t, J = 6.2 Hz, 2H), 5.48 (brs, 1H). The redundant peaks of 1.45 and 1.46 and 2.85 and 2.90 are due to the existence of carbamate rotamers. ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.1 and 210.4, 155.7, 136.2 and 135.8, 120.1 and 119.8, 79.4, 47.6 and 46.5, 39.6, 38.6, 35.6 and 34.9, 34.0, 28.4. The redundant peaks are due to the rotation of the C−N bond in the molecule. IR (neat): ν 2975, 2931, 1692, 1482, 1396, 1366, 1158, 1052, 882, 771 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{23}NO_3Na^+$ (M + Na$^+$): 276.1570. Found: 276.1565.

When this [5 + 1] reaction was carried out under 5 atm of CO, the reaction yields were 52% and 56% (two times tests) (**3c**: 22.4 mg, 15 mol % of Rh(dppp)OTf, 48 h, obtained **2c**: 13.1 mg, 52% yield; **3c**: 31.8 mg, 15 mol % of Rh(dppp)OTf, 48 h, obtained **2c**: 20.0 mg, 56% yield).

*(±)-tert-Butyl (2-(3′,4′-Dimethoxy-4-oxo-3,4-dihydro[1,1′-biphenyl]-1(2H)-yl)ethyl) Methylcarbamate [(±)-**1c**].* A suspension of $Pd(OAc)_2$ (3.0 mg, 0.0134 mmol), dppe (10.7 mg, 0.0269 mmol), and Cs_2CO_3 (65.5 mg, 0.20 mmol) in toluene (1.0 mL) was stirred in a 100 °C oil bath for 10 min. Then a solution of **5** (20.3 mg, 0.0935 mmol) in toluene (1.0 mL) was added. After the suspension was stirred for 5 min, a solution of **2c** (33.9 mg, 0.134 mmol) in toluene (1.0 mL) was added. The reaction mixture was heated at 100 °C for 4 h. Then the reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 3:1) afforded product (±)-**1c** as a colorless oil (25.3 mg, 68% yield, calculated based on the amount of **5**). This reaction gave also some unidentified side products, judged from TLC.

(±)-**1c**. Colorless oil. TLC R_f (PE/EA 2:1) = 0.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.96−2.06 (m, 1H), 2.06−2.16 (m, 1H), 2.20−2.31 (m, 3H), 2.31−2.42 (m, 1H), 2.78 (s, 3H), 3.03 (brs, 1H), 3.13−3.25 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 6.18 (d, J = 10.0 Hz, 1H), 6.84 (brs, 3H), 7.11 (d, J = 10.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 155.4, 154.6, 149.1, 147.9, 135.0, 129.6, 119.0, 111.1, 109.8, 79.5, 56.0 and 55.8, 44.9, 42.5, 38.9 and 38.5, 36.1, 34.4, 28.4. The redundant peaks are due to the rotation of the C−N bond in the molecule. IR (neat): ν 2972, 2935, 2868, 2837, 1688, 1518, 1395,

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1366, 1259, 1174, 1149, 1027, 881, 770 cm^{-1}. HRMS (ESI): calcd for $C_{22}H_{31}NO_5Na^+$ (M + Na^+): 412.2094. Found: 412.2086.

*tert-Butyl (R)-(2-(3′,4′-Dimethoxy-4-oxo-3,4-dihydro[1,1′-biphenyl]-1(2H)-yl)ethyl) Methylcarbamate [(R)-**1c**].* A suspension of $Pd(OAc)_2$ (5.7 mg, 0.0254 mmol), (*S*)-Antphos (9.4 mg, 0.0254 mmol), and Cs_2CO_3 (62.1 mg, 0.191 mmol) in toluene (1.0 mL) was stirred in 100 °C oil bath for 10 min. Then a solution of **5** (13.2 mg, 0.061 mmol) in toluene (1.0 mL) was added. After 5 min of stirring, a solution of **2c** (32.1 mg, 0.127 mmol) in toluene (1.0 mL) was added. The reaction mixture was heated at 100 °C for 4 h. Then the reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with PE/EA 3:1) afforded product (*R*)-**1c** as a colorless oil (15.9 mg, 63% yield, calculated based on the amount of **5**). This reaction gave also some unidentified side products, judged from TLC.

(−)-Mesembrine.[4h,l] To a solution of (*R*)-**1c** (15.9 mg, 0.0397 mmol) in DCM (3.0 mL) was added TFA (46.0 mg, 0.400 mmol). After stirring at room temperature for 12 h, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and extracted with DCM. The combined organic phase was dried with anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with DCM/EtOH 20:1) afforded product (−)-mesembrine as a colorless oil (8.4 mg, 73% yield) in 86% ee.

(−)-Mesembrine. Colorless oil. TLC R_f (DCM/MeOH 10:1) = 0.55. $[\alpha]_D^{20}$ = −60.5 (*c* = 0.42, $CHCl_3$) (lit.[4h] $[\alpha]_D^{20}$ = −61.6 (*c* = 0.25, MeOH)). ^1H NMR (400 MHz, $CDCl_3$): δ 2.07−2.26 (m, 5H), 2.29−2.48 (m, 2H), 2.33 (s, 3H), 2.61 (d, *J* = 3.6 Hz, 2H), 2.97 (t, *J* = 3.6 Hz, 1H), 3.12−3.19 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.4, 149.0, 147.5, 140.0, 117.9, 111.0, 109.9, 70.3, 56.0, 55.9, 54.8, 47.5, 40.5, 40.1, 38.8, 36.2, 35.2. IR (neat): ν 2926, 2847, 2783, 1717, 1645, 1592, 1517, 1457, 1413, 1327, 1258, 1180, 1147, 1028, 809, 765 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{24}NO_3^+$ (M + H^+) 290.1751, found 290.1744. The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALPAK AS-H, 4.6 × 250 mm, eluent = *n*-hexane/2-propanol = 80:20, 1.00 mL·min−1, λ = 220 nm) t_R (major) = 10.6 min, t_R (minor) = 8.9 min.

(±)-Mesembrine. To a solution of (±)-**1c** (31.4 mg, 0.081 mmol) in DCM (2.5 mL) was added TFA (89.0 mg, 0.78 mmol). After being stirred at room temperature for 22 h, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and extracted with DCM. The combined organic phase was dried with anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue via column chromatography on silica gel (eluted with DCM/EtOH 20:1) afforded product (±)-mesembrine as a colorless oil (17.8 mg, 76% yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01908.

NMR spectra for all new compounds and HPLC chromatogram data (PDF)

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Notes

The authors declare no competing financial interest.

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