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Stereoselective Construction of Spiro-Fused Tricyclic Frameworks by Sequential Reaction of Enynes, Imines, and Diazoalkenes with Rh(I) and Rh(II) Catalysts

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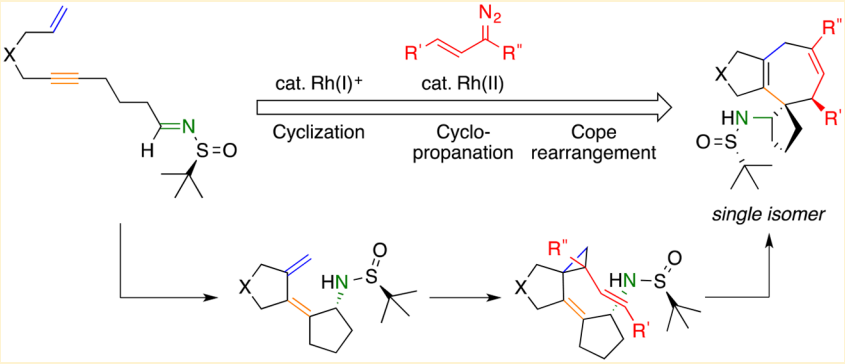
Supporting Information



ABSTRACT: Stereoselective construction of spiro-fused tricyclic compounds from enynes having a tethered imine with diazoalkenes was achieved by Rh(I)- and Rh(II)-catalyzed sequential reactions. This method consists of three reactions, i.e., Rh(I)-catalyzed cyclization of enynes with a tethered imine, Rh(II)-catalyzed cyclopropanation with diazoalkenes, and Cope rearrangement. Notably, the sequential reactions can be operated in one pot, in which Rh(I) and Rh(II) catalysts work in relay without any serious catalyst deactivation to afford the spirocycles in a stereoselective manner.

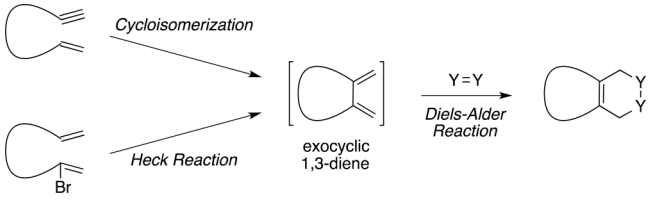
INTRODUCTION

The development of methods for constructing polycyclic molecules in a stereoselective manner has been a substantial challenge in synthetic organic chemistry. One approach to this goal is the use of sequential reactions, which allow multiple reactions to occur in a single operation, resulting in the construction of complex skeletons from readily available starting materials.[1] One-pot reactions involving exocyclic 1,3-dienes as intermediates have emerged as powerful tools for the synthesis of polycyclic compounds because exocyclic dienes are suitable substrates of the Diels–Alder reaction and can be efficiently prepared by transition metal-catalyzed reactions such as cycloisomerization of enynes and intramolecular Heck reaction (Scheme 1).[2]

During the course of our study of the reactivity of oxa- and azarhodacycle intermediates,[3] we have recently found a Rh(I)-catalyzed cyclization of enynes (*S*)-**1** with tethered imines to give five-membered cyclic compounds **2** possessing exocyclic 1,3-diene moieties through *β*-hydride elimination from azarhodacycle intermediate **I** (Scheme 2).[4] Furthermore, we showed that products **2** had reacted with various dienophiles in one pot to afford spiro-fused polycyclic compounds **3** through the Diels–Alder reaction. Notably, both the Rh(I)-catalyzed cyclization and the Diels–Alder reaction proceeded in a highly stereoselective manner by virtue of the tethered (*S*)-*tert*-butanesulfinamide moiety, producing the spirocycles **3** as single isomers.

To date, however, most of the one-pot processes using exocyclic 1,3-dienes as intermediates rely upon the Diels–Alder

Scheme 1. Exocyclic 1,3-Dienes as Versatile Precursors of Polycyclic Compounds



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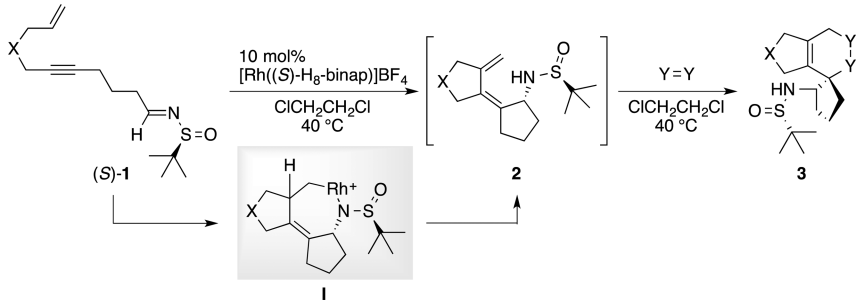
Scheme 2. Stereoselective Synthesis of Spirocycles 3



Scheme 3. Tandem Cyclopropanation/Cope Rearrangement

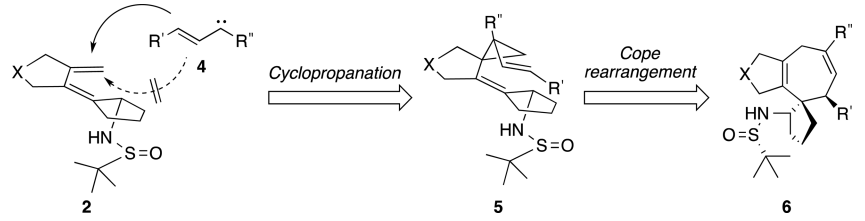
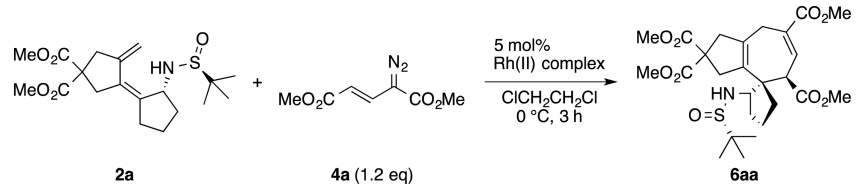


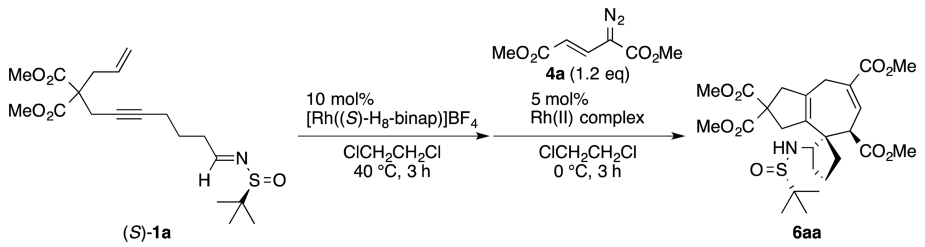
Table 1. Screening of Rh(II) Catalysts



		yield (%)	
entry	Rh(II) complex[a]	**6aa**	rec. **2a**
1	$Rh_2(OAc)_4$	–	96
2	$Rh_2(TFA)_4$	–	89
3	$Rh_2(oct)_4$	36	50
4	$Rh_2(TPA)_4$	60	trace
5	$Rh_2(piv)_4$	72	trace
6	$Rh_2(esp)_2$	79	trace

[a]Abbreviations: $Rh_2(OAc)_4$, rhodium acetate dimer; $Rh_2(TFA)_4$, rhodium trifluoroacetate dimer; $Rh_2(oct)_4$, rhodium octanoate dimer; $Rh_2(TPA)_4$, rhodium triphenylacetate dimer; $Rh_2(piv)_4$, rhodium pivalate dimer; $Rh_2(esp)_2$, bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)].

Table 2. One-Pot Synthesis of 6aa Directly from (*S*)-1a



		yield (%)	
entry	Rh(II) complex	**6aa**	**2a**
1	$Rh_2(piv)_4$	53	<26
2	$Rh_2(esp)_2$	62	<11

reaction to convert the diene into polycyclic compounds. We therefore decided to explore a novel usage of exocyclic 1,3-dienes.

Because the Diels–Alder reaction of compound **2** proceeded with complete stereoselectivity, it is thought that a bulky (*S*)-*tert*-butanesulfinamide moiety effectively shields one side of the diene **2**. Thus, if the reaction between the diene **2** and a vinylcarbenoid **4** is to be performed, cyclopropanation would occur on the less-hindered side of the diene **2** to afford divinylcyclopropane **5**. Subsequently, if the divinylcyclopropane

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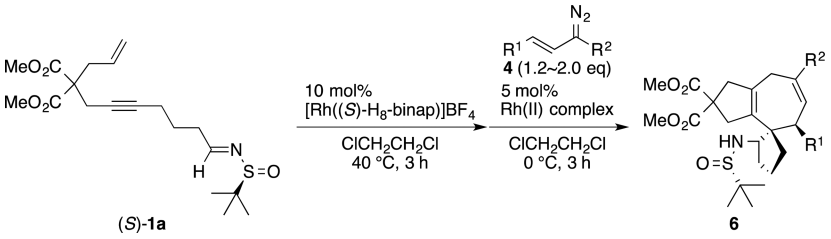
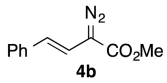
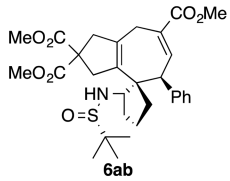
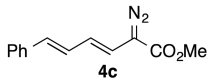
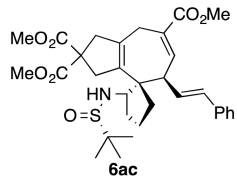
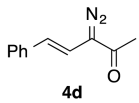
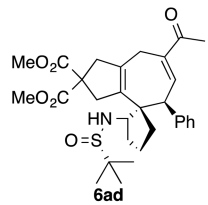
Table 3. Sequential Reaction with Various Vinyldiazo Compounds 4



entry	substrate **4**	**4** (eq)	Rh(II)	product **6**	yield (%)
1	 **4b**	1.8	$Rh_2(piv)_4$	 **6ab**	81
2		1.8	$Rh_2(esp)_2$		70
3	 **4c**	1.5	$Rh_2(piv)_4$	 **6ac**	81
4		1.8	$Rh_2(esp)_2$		77
5	 **4d**	1.2	$Rh_2(piv)_4$	 **6ad**	36
6		1.2	$Rh_2(esp)_2$		60
7		2.0	$Rh_2(esp)_2$[a]		72

[a] $Rh_2(esp)_2$ (10 mol %) was used.

5 is to undergo a Cope rearrangement, the spirocycle **6** with a seven-membered ring could be formed stereoselectively (Scheme 3).[5,6] Herein, we disclose our attempt to realize the envisaged sequential process.

RESULTS AND DISCUSSION

Initially, the reaction between diene **2a** and vinyldiazoacetate **4a** in $ClCH_2CH_2Cl$ at 0 °C was conducted using various Rh(II) catalysts at 5 mol % (Table 1). In the presence of $Rh_2(OAc)_4$, the reaction did not proceed at all (entry 1). $Rh_2(TFA)_4$ was also ineffective, and the diene **2a** was recovered in 89% yield (entry 2). On the other hand, $Rh_2(oct)_4$ afforded the desired spirocycle **6aa** in 36% yield, even though 50% of the diene **2a** was recovered (entry 3). When $Rh_2(TPA)_4$ was used, almost all of the diene **2a** was consumed and the yield of **6aa** was improved to 60% yield (entry 4). Further investigation showed that the use of $Rh_2(piv)_4$ and $Rh_2(esp)_2$ gave the spirocycle **6aa** in 72 and 79% yields, respectively (entries 5 and 6, respectively). In these reactions, the spirocycle **6aa** was obtained as a single isomer.

Next, the one-pot synthesis of spirocycle **6aa** directly from (*S*)-**1a** was attempted to establish the sequential process (Table 2). A solution of enyne (*S*)-**1a** and [Rh((*S*)-H_8-binap)]BF_4 (10 mol %) in $ClCH_2CH_2Cl$ was stirred at 40 °C for 3 h, generating the diene **2a** in situ. After the reaction mixture had been cooled to 0 °C, the vinyldiazoacetate **4a** (1.2 equiv) and Rh(II) complex (5.0 mol %) were added to the same reaction vessel, and the mixture was stirred for an additional 3 h. As a result, it was found that when $Rh_2(piv)_4$ and $Rh_2(esp)_2$ were used as Rh(II) catalysts, the spirocycle **6aa** was obtained in 53 and 62% yields, respectively.

To delineate the scope of the method presented here, a variety of vinyldiazo compounds **4** were subjected to the sequential reaction from the enyne (*S*)-**1a** (Table 3). Vinyldiazo compounds **4b** and **4c**, possessing a phenyl group and a styryl group at the vinyl terminus, afforded the spirocycles **6ab** and **6ac**, respectively, in good yields using $Rh_2(piv)_4$ or $Rh_2(esp)_2$ as a Rh(II) catalyst (entries 1−4). On the other hand, the reactions of vinyldiazo compound **4d**, having a ketone moiety, were rather sluggish (entries 5 and 6). It was found that the yield of the spirocycle **6ad** was improved to 72% when 2.0 equiv of vinyldiazo compound **4d** was reacted in the presence of 10 mol % $Rh_2(esp)_2$ (entry 7).

The reaction scope was also examined with respect to enynes (*S*)-**1** (Table 4). The reaction from enynes (*S*)-**1b**, **1c**, and **1d** possessing benzyloxy, acetoxy, and fluorene moieties in a tether proceeded well to afford the spirocycles **6bb**, **6cb**, and **6db**, respectively, in good yields (entries 1−6). On the other hand, the reaction from (*S*)-**1e** having a heteroatom in the chain resulted in a lower yield, probably because of the modest yield of the diene **2e** generated in situ at the first step of Rh(I)-catalyzed cyclization of (*S*)-**1e** (entries 7 and 8).[4]

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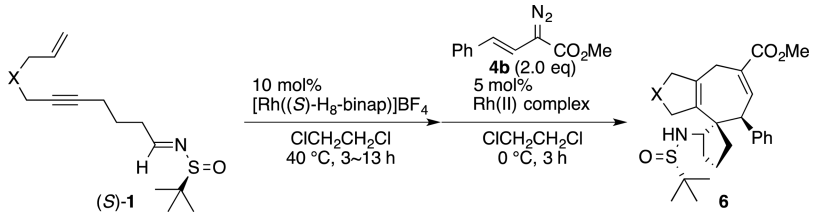
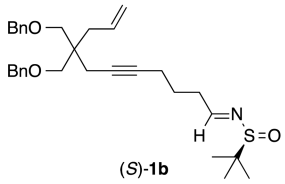
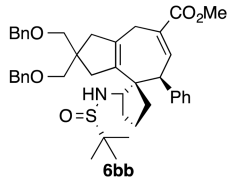
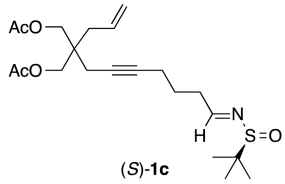
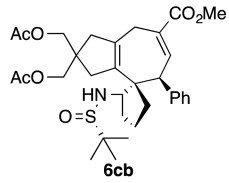
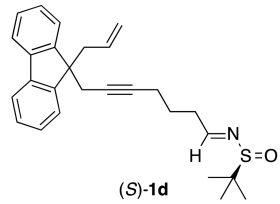
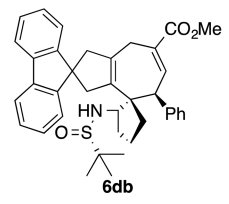
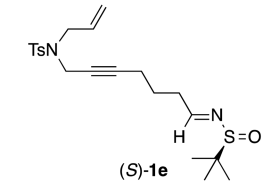
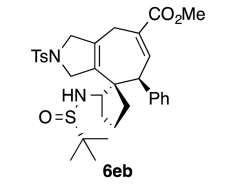
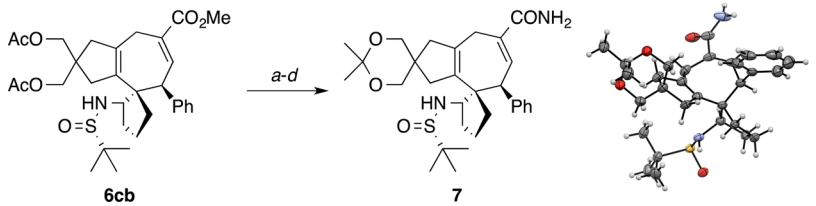
Table 4. One-Pot Synthesis of Spirocycles 6 from Various Enynes (*S*)-1



entry	substrate (*S*)-**1**	Rh(II)	product **6**	yield (%)
1	 (*S*)-**1b**	$Rh_2(piv)_4$	 **6bb**	69
2		$Rh_2(esp)_2$		65
3	 (*S*)-**1c**	$Rh_2(piv)_4$	 **6cb**	88
4		$Rh_2(esp)_2$		80
5	 (*S*)-**1d**	$Rh_2(piv)_4$	 **6db**	74
6		$Rh_2(esp)_2$		82
7	 (*S*)-**1e**	$Rh_2(piv)_4$	 **6eb**	45
8		$Rh_2(esp)_2$		42

Scheme 4. Synthesis and X-ray Crystal Structure Analysis of 7[a]



[a]Conditions: (a) K_2CO_3, MeOH; (b) 2,2-dimethoxypropane, PPTS, CH_2Cl_2/acetone; (c) aq NaOH, THF/MeOH; (d) NH_4Cl, HATU, iPr_2NEt, DMF, 55% (four steps). Note that for the ORTEP diagram of **7**, three crystallographically independent molecules of **7** are contained in a unit cell. There is essentially no difference among the structures of the three molecules. Disordered MeOAc molecules included as a solvent of crystallization have been omitted for the sake of clarity. The ellipsoid contour percent probability level is 50%.

In the one-pot reactions we conducted, all of the products were obtained as single stereoisomers. To determine the stereochemistry of spirocycles **6**, the product **6cb** was converted to compound **7**, which could be recrystallized from a hexane/methyl acetate solution (Scheme 4). By X-ray analysis of **7**,[7] both relative and absolute configurations of spirocycle **6cb** were unambiguously established as depicted in Scheme 4.[8] These results confirmed that the sequential processes from enyne (*S*)-**1** proceeded in a stereoselective manner as initially planned (Scheme 3).

CONCLUSION

We have succeeded in developing a new method for the stereoselective synthesis of spirocycles **6** starting from enynes (*S*)-**1**. This method consists of three reactions, i.e., Rh(I)-catalyzed cyclization of enynes with a tethered imine, Rh(II)-

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catalyzed cyclopropanation with diazoalkenes, and Cope rearrangement. Notably, two different catalysts, Rh(I) and Rh(II), work in relay without any serious catalyst deactivation in one pot, making this sequential transformation operative. The polycyclic products have distinctive spiro-fused frameworks, which may have various applications in forms such as ligands, organocatalysts, and bioactive scaffolds.

EXPERIMENTAL SECTION

General. Reactions including air- or moisture-sensitive compounds were performed in a dry vessel under an argon atmosphere. Solvents (THF, Et_2O, toluene, DMF, and CH_3CN) were purified under an argon atmosphere using a solvent purification system. 1,2-Dichloroethane was distilled under an argon atmosphere from CaH_2. NMR spectra were recorded on 500 MHz (^1H) and 125 or 100 MHz (^{13}C) instruments. Chemical shifts (δ) were reported in parts per million, relative to the solvent residual peak ($CDCl_3$; 7.26 ppm for ^1H and 77.16 ppm for ^{13}C). Data for ^1H NMR were reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad signal; m, multiplet; app, apparent), coupling constants (J) in hertz, and integration. High-resolution mass spectra were obtained with ESI-HRMS (orbitrap) instruments. Column chromatography was performed with an automated flash chromatography system.

Synthesis of Substrates. The enynes (*S*)-**1**,[1] the cyclic compound **2a**,[4] and the diazo compounds (**4a**,[9] **4b**,[9,10] **4c**,[11] and **4d**[10]) were prepared according to the reported procedures.

Synthesis and Spectral Data of Cyclized Compounds. *Tetramethyl (2′R,4S,5R)-2′-{[(S)-tert-Butylsulfinyl]amino}-1,3,5,8-tetrahydro-2H-spiro[azulene-4,1′-cyclopentane]-2,2,5,7-tetracarboxylate (**6aa**).* ^1H NMR (500 MHz, $CDCl_3$) δ: 7.06 (d, J = 8.5 Hz, 1H), 3.73 (d, J = 1.0 Hz, 6H), 3.72 (s, 3H), 3.66 (s, 3H), 3.52−3.50 (m, 3H), 3.21 (d, J = 16.6 Hz, 1H), 3.15−2.98 (m, 4H), 2.86 (d, J = 16.8 Hz, 1H), 2.26−2.19 (m, 1H), 2.08−2.03 (m, 1H), 1.91−1.75 (m, 3H), 1.71−1.61 (m, 1H), 1.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.9, 171.8, 171.4, 167.0, 137.0, 133.9, 133.3, 131.2, 66.9, 56.5, 55.8, 53.0, 52.9, 52.8, 52.2, 52.1, 52.1, 46.7, 45.4, 34.5, 33.2, 29.4, 22.8 (3C), 20.8. IR (neat) $\tilde{\nu}$: 3278, 2954, 1731, 1659 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{26}H_{37}NNaO_9S^+$ [$(M + Na)^+$] 562.2081, found 562.2078. $[\alpha]_D^{23}$: − 66.7 (c 4.04, $CHCl_3$).

To a solution of **2a** (40.8 mg, 0.106 mmol) and $Rh_2(OAc)_4$ (2.35 mg, 0.00532 mmol) in $ClCH_2CH_2Cl$ (0.41 mL, degassed by three freeze−pump up−thaw cycles) was added **4a** (23.5 mg, 0.128 mmol) in $ClCH_2CH_2Cl$ (0.65 mL, degassed by three freeze−pump up−thaw cycles) at 0 °C by cannulation under argon gas. The reaction mixture was stirred at 0 °C for 3 h under argon gas. The reaction mixture was concentrated and purified by silica gel column chromatography (40:60 to 0:100 hexane/EtOAc) to give **2a** (39.0 mg, 96% yield) as a colorless oil.

To a solution of **2a** (16.7 mg, 0.435 mmol) and $Rh_2(TFA)_4$ (1.43 mg, 0.00218 mmol) in $ClCH_2CH_2Cl$ (0.17 mL, degassed by three freeze−pump up−thaw cycles) was added **4a** (9.62 mg, 0.523 mmol) in $ClCH_2CH_2Cl$ (0.27 mL, degassed by three freeze−pump up−thaw cycles) at 0 °C by cannulation under argon gas. The reaction mixture was stirred at 0 °C for 3 h under argon gas. The reaction mixture was concentrated and purified by silica gel column chromatography (40:60 to 0:100 hexane/EtOAc) to give **2a** (14.8 mg, 89% yield) as a colorless oil.

To a solution of **2a** (37.4 mg, 0.0975 mmol) and $Rh_2(oct)_4$ (3.80 mg, 0.00488 mmol) in $ClCH_2CH_2Cl$ (0.38 mL, degassed by three freeze−pump up−thaw cycles) was added **4a** (21.6 mg, 0.117 mmol) in $ClCH_2CH_2Cl$ (0.60 mL, degassed by three freeze−pump up−thaw cycles) at 0 °C by cannulation under argon gas. The reaction mixture was stirred at 0 °C for 3 h under argon gas. The reaction mixture was concentrated and purified by silica gel column chromatography (40:60 to 0:100 hexane/EtOAc) to give **6aa** (18.9 mg, 36% yield) as a colorless oil and **2a** (18.8 mg, 50% yield) as a colorless oil.

To a solution of **2a** (42.3 mg, 0.110 mmol) and $Rh_2(TPA)_4$ (7.47 mg, 0.00551 mmol) in $ClCH_2CH_2Cl$ (0.43 mL, degassed by three freeze−pump up−thaw cycles) was added **4a** (24.4 mg, 0.132 mmol) in $ClCH_2CH_2Cl$ (0.68 mL, degassed by three freeze−pump up−thaw cycles) at 0 °C by cannulation under argon gas. The reaction mixture was stirred at 0 °C for 3 h under argon gas. The reaction mixture was concentrated and purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6aa** (35.9 mg, 60% yield) as a colorless oil and **2a** (<2.2 mg, <5% yield) as a colorless oil.

To a solution of **2a** (24.9 mg, 0.0649 mmol) and $Rh_2(piv)_4$ (1.98 mg, 0.00325 mmol) in $ClCH_2CH_2Cl$ (0.25 mL, degassed by three freeze−pump up−thaw cycles) was added **4a** (14.4 mg, 0.0779 mmol) in $ClCH_2CH_2Cl$ (0.40 mL, degassed by three freeze−pump up−thaw cycles) at 0 °C by cannulation under argon gas. The reaction mixture was stirred at 0 °C for 3 h under argon gas. The reaction mixture was concentrated and purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6aa** (25.2 mg, 72% yield) as a colorless oil and **2a** (<4.5 mg, <18% yield) as a colorless oil.

To a solution of **2a** (25.9 mg, 0.0675 mmol) and $Rh_2(esp)_2$ (2.56 mg, 0.00338 mmol) in $ClCH_2CH_2Cl$ (0.26 mL, degassed by three freeze−pump up−thaw cycles) was added **4a** (14.9 mg, 0.0810 mmol) in $ClCH_2CH_2Cl$ (0.41 mL, degassed by three freeze−pump up−thaw cycles) at 0 °C by cannulation under argon gas. The reaction mixture was stirred at 0 °C for 3 h under argon gas. The reaction mixture was concentrated and purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6aa** (28.9 mg, 79% yield) as a colorless oil and **2a** (<2.6 mg, <10% yield) as a colorless oil.

General Procedure for One-Pot Synthesis of 6aa from (*S*)-1a. A solution of $[Rh(cod)_2]BF_4$[12] (6.09 mg, 0.0150 mmol, 10 mol % to a substrate) and (*S*)-H_8-BINAP (9.46 mg, 0.0150 mmol, 10 mol % to a substrate) in $ClCH_2CH_2Cl$ (0.58 mL, 0.026 M to Rh, degassed by three freeze−pump up−thaw cycles) was stirred under a H_2 atmosphere at rt for 1 h. Then the reaction mixture was degassed by three freeze−pump up−thaw cycles, and the reaction vessel was filled with argon gas. To the mixture was added a solution of (*S*)-**1a** (57.5 mg, 0.150 mmol, 1 equiv) in $ClCH_2CH_2Cl$ (0.92 mL, 0.16 M to a substrate, degassed by three freeze−pump up−thaw cycles) by cannulation under argon gas, and the reaction mixture was stirred at 40 °C for 3 h. To the mixture were added **4a** (33.1 mg, 0.180 mmol, 1.2 equiv) and the Rh(II) complex (0.00750 mmol, 5 mol % to a substrate) at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h. After removal of the solvent, the residue was purified by silica gel column chromatography to give product **6aa**.

According to the general procedure for one-pot synthesis of **6aa**, a crude product, which was prepared from (*S*)-**1a**, **4a**, and $Rh_2(piv)_4$ (4.58 mg, 0.00750 mmol), was purified by silica gel column chromatography (40:60 to 0:100 hexane/EtOAc) to give **6aa** (43.2 mg, 53% yield) as a colorless oil and **2a** (<14.8 mg, <26% yield) as a pale yellow oil.

According to the general procedure for one-pot synthesis of **6aa**, a crude product, which was prepared from (*S*)-**1a**, **4a**, and $Rh_2(esp)_2$ (5.69 mg, 0.00750 mmol), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6aa** (49.8 mg, 62% yield) as a colorless oil and **2a** (<6.5 mg, <11% yield) as a pale yellow oil.

General Procedure for One-Pot Synthesis of 6a from (*S*)-1a. A solution of $[Rh(cod)_2]BF_4$[12] (6.09 mg, 0.0150 mmol, 10 mol % to a substrate) and (*S*)-H_8-BINAP (9.46 mg, 0.0150 mmol, 10 mol % to a substrate) in $ClCH_2CH_2Cl$ (0.58 mL, 0.026 M to Rh, degassed by three freeze−pump up−thaw cycles) was stirred under a H_2 atmosphere at rt for 1 h. Then the reaction mixture was degassed by three freeze−pump up−thaw cycles, and the reaction vessel was filled with argon gas. To the mixture was added a solution of (*S*)-**1a** (57.5 mg, 0.150 mmol, 1 equiv) in $ClCH_2CH_2Cl$ (0.92 mL, 0.16 M to a substrate, degassed by three freeze−pump up−thaw cycles) by cannulation under argon gas, and the reaction mixture was stirred at 40 °C for 3 h. To the mixture were added **4** and the Rh(II) complex (0.00750 mmol, 5 mol % to a substrate) at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h. After removal of the solvent, the residue was purified by silica gel column chromatography to give a product **6a**.

Trimethyl (2′R,4S,5S)-2′-{[(S)-tert-Butylsulfinyl]amino}-5-phenyl-1,3,5,8-tetrahydro-2H-spiro[azulene-4,1′-cyclopentane]-2,2,7-tri-

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*carboxylate (**6ab**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25−7.20 (m, 3H), 7.11−7.08 (m, 3H), 3.99 (t, J = 6.6 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.44 (d, J = 5.9 Hz, 1H), 3.37−3.28 (m, 2H), 3.21 (d, J = 20.8 Hz, 1H), 3.08 (d, J = 14.9 Hz, 2H), 2.93 (d, J = 16.6 Hz, 1H), 2.41 (d, J = 16.6 Hz, 1H), 2.32−2.25 (m, 1H), 2.02−1.96 (m, 1H), 1.85−1.59 (m, 4H), 1.16 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.6, 172.2, 168.2, 141.9, 139.0, 135.4, 131.6, 130.3 (2C), 128.3 (2C), 127.9, 127.3, 64.8, 56.7, 55.9, 55.4, 53.0, 52.9, 52.2, 50.1, 46.9, 46.0, 32.7, 31.8, 29.5, 22.7 (3C), 20.0. IR (neat) $\tilde{\nu}$: 3281, 3025, 2953, 1732, 1650, 1599 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{30}H_{39}NNaO_7S^+$ [(M + Na)$^+$] 580.2339, found 580.2343. $[\alpha]_D^{22}$: − 153.2 (c 4.19, $CHCl_3$).

According to the general procedure for one-pot synthesis of **6a**, a crude product, which was prepared from (*S*)-**1a**, **4b** (54.6 mg, 0.270 mmol, 1.8 equiv), and $Rh_2(piv)_4$ (4.58 mg, 0.00750 mmol), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6ab** (67.4 mg, 81% yield) as a colorless oil.

According to the general procedure for one-pot synthesis of **6a**, a crude product, which was prepared from (*S*)-**1a**, **4b** (54.6 mg, 0.270 mmol, 1.8 equiv), and $Rh_2(esp)_2$ (5.69 mg, 0.00750 mmol), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6ab** (58.6 mg, 70% yield) as a colorless oil.

*Trimethyl (2′R,4S,5R)-2′-{[(S)-tert-Butylsulfinyl]amino}-5-[(E)-styryl]-1,3,5,8-tetrahydro-2H-spiro[azulene-4,1′-cyclopentane]-2,2,7-tricarboxylate (**6ac**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.21 (t, J = 7.1 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.40 (d, J = 15.6 Hz, 1H), 6.02 (dd, J = 15.4, 9.0 Hz, 1H), 3.82−3.79 (m, 1H), 3.72 (s, 6H), 3.69 (s, 3H), 3.26−2.98 (m, 8H), 2.25−2.22 (m, 1H), 1.89−1.81 (m, 4H), 1.72−1.67 (m, 1H), 1.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5, 172.3, 167.8, 141.2, 137.0, 134.8, 133.0, 131.2, 128.5 (2C), 127.8 (2C), 127.5, 126.4 (2C), 65.3, 56.9, 55.7, 54.5, 52.9, 52.9, 52.0, 50.1, 46.9, 46.2, 33.8, 32.7, 30.1, 22.7 (3C), 20.2. IR (neat) $\tilde{\nu}$: 3280, 2953, 1731, 1714, 1652, 1599 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{32}H_{41}NNaO_7S^+$ [(M + Na)$^+$] 606.2496, found 606.2488. $[\alpha]_D^{26}$: − 161.4 (c 6.81, $CHCl_3$).

According to the general procedure for one-pot synthesis of **6a**, a crude product, which was prepared from (*S*)-**1a**, **4c** (51.4 mg, 0.225 mmol, 1.5 equiv), and $Rh_2(piv)_4$ (4.58 mg, 0.00750 mmol), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6ac** (70.5 mg, 81% yield) as a colorless oil.

According to the general procedure for one-pot synthesis of **6a**, a crude product, which was prepared from (*S*)-**1a**, **4c** (61.6 mg, 0.270 mmol, 1.8 equiv), and $Rh_2(esp)_2$ (5.69 mg, 0.00750 mmol), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6ac** (67.7 mg, 77% yield) as a colorless oil.

*Dimethyl (2′R,4S,5S)-7-Acetyl-2′-{[(S)-tert-butylsulfinyl]amino}-5-phenyl-1,3,5,8-tetrahydro-2H-spiro[azulene-4,1′-cyclopentane]-2,2-dicarboxylate (**6ad**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29−7.23 (m, 3H), 7.13 (d, J = 6.3 Hz, 2H), 6.94 (d, J = 6.3 Hz, 1H), 3.93 (s, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.54−3.51 (m, 1H), 3.34 (s, 1H), 3.30 (d, J = 6.8 Hz, 1H), 3.16 (d, J = 9.0 Hz, 1H), 3.08 (d, J = 17.1 Hz, 2H), 2.92 (d, J = 17.6 Hz, 1H), 2.44 (d, J = 14.9 Hz, 1H), 2.29 (s, 4H), 2.05−1.97 (m, 1H), 1.86−1.81 (m, 1H), 1.72−1.62 (m, 3H), 1.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.4, 172.6, 172.1, 143.3, 139.0, 137.7, 135.0, 132.0, 130.2 (2C), 128.3 (2C), 127.3, 64.7, 56.6, 55.9, 55.2, 52.9, 52.8, 50.3, 46.8, 45.8, 32.8, 31.8, 27.6, 25.5, 22.7 (3C), 20.0. IR (neat) $\tilde{\nu}$: 3283, 2955, 1732, 1666, 1599 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{30}H_{39}NNaO_6S^+$ [(M + Na)$^+$] 564.2390, found 564.2397. $[\alpha]_D^{26}$: − 153.0 (c 5.42, $CHCl_3$).

According to the general procedure for one-pot synthesis of **6a**, a crude product, which was prepared from (*S*)-**1a**, **4d** (33.5 mg, 0.180 mmol, 1.2 equiv), and $Rh_2(piv)_4$ (4.58 mg, 0.00750 mmol), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6ad** (28.9 mg, 36% yield) as a colorless oil and **2a** (21.6 mg, 38% yield) as a pale yellow oil.

According to the general procedure for one-pot synthesis of **6a**, a crude product, which was prepared from (*S*)-**1a**, **4d** (33.5 mg, 0.180 mmol, 1.2 equiv), and $Rh_2(esp)_2$ (5.69 mg, 0.00750 mmol), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6ad** (49.0 mg, 60% yield) as a colorless oil and **2a** (16.1 mg, 28% yield) as a pale yellow oil.

According to the general procedure for one-pot synthesis of **6a**, a crude product, which was prepared from (*S*)-**1a**, **4d** (55.9 mg, 0.300 mmol, 2.0 equiv), and $Rh_2(esp)_2$ (11.4 mg, 0.0150 mmol), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6ad** (58.3 mg, 72% yield) as a colorless oil and **2a** (5.5 mg, 10% yield) as a pale yellow oil.

General Procedure for One-Pot Synthesis of 6 from (*S*)-1. A solution of $[Rh(cod)_2]BF_4$[12] (6.09 mg, 0.0150 mmol, 10 mol % to a substrate) and (*S*)-H_8-BINAP (9.46 mg, 0.0150 mmol, 10 mol % to a substrate) in $ClCH_2CH_2Cl$ (0.58 mL, 0.026 M to Rh, degassed by three freeze−pump up−thaw cycles) was stirred under a H_2 atmosphere at room temperature for 1 h. Then the reaction mixture was degassed by three freeze−pump up−thaw cycles, and the reaction vessel was filled with argon gas. To the mixture was added a solution of (*S*)-**1** (0.150 mmol, 1 equiv) in $ClCH_2CH_2Cl$ (0.92 mL, 0.16 M to a substrate, degassed by three freeze−pump up−thaw cycles) by cannulation under argon gas, and the reaction mixture was stirred at 40 °C for the indicated time. To the mixture were added **4b** (60.7 mg, 0.300 mmol, 2.0 equiv) and the Rh(II) complex (0.00750 mmol, 5 mol % to a substrate) at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h. After removal of the solvent, the residue was purified by silica gel column chromatography to give a product **6**.

*Methyl (2′R,4S,5S)-2,2-Bis[(benzyloxy)methyl]-2′-{[(S)-tert-butylsulfinyl]amino}-5-phenyl-2,3,5,8-tetrahydro-1H-spiro[azulene-4,1′-cyclopentane]-7-carboxylate (**6bb**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33−7.07 (m, 16H), 4.46 (s, 2H), 4.42 (dd, J = 16.6, 12.5 Hz, 2H), 3.98 (t, J = 6.7 Hz, 1H), 3.72 (s, 3H), 3.42 (d, J = 7.3 Hz, 1H), 3.37−3.15 (m, 6H), 2.97 (d, J = 9.1 Hz, 1H), 2.42 (d, J = 17.6 Hz, 1H), 2.37 (d, J = 17.6 Hz, 1H), 2.27−2.21 (m, 1H), 2.15 (d, J = 16.9 Hz, 1H), 2.02−2.01 (m, 1H), 1.82−1.57 (m, 5H), 1.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.4, 141.7, 139.0, 138.8, 138.7, 135.8, 132.4, 130.5 (2C), 128.3 (2C), 128.3 (3C), 128.0 (2C), 127.6 (2C), 127.5 (3C), 127.5, 127.2, 74.1, 73.8, 73.2 (2C), 64.8, 55.7, 55.7, 52.1, 49.8, 46.3, 45.3, 44.3, 32.3, 31.7, 30.3, 22.6 (3C), 19.8. IR (neat) $\tilde{\nu}$: 3417, 3027, 2952, 2886, 2853, 1711, 1650, 1600 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{42}H_{51}NNaO_5S^+$ [(M + Na)$^+$] 704.3380, found 704.3377. $[\alpha]_D^{27}$: − 88.6 (c 8.02, $CHCl_3$).

According to the general procedure for one-pot synthesis of **6**, a crude product, which was prepared from (*S*)-**1b** (76.2 mg, 0.150 mmol), **4b**, and $Rh_2(piv)_4$ (4.58 mg, 0.00750 mmol) at 40 °C for 3 h (the first step) and at 0 °C for 3 h (the second step), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6bb** (70.2 mg, 69% yield) as a colorless oil.

According to the general procedure for one-pot synthesis of **6**, a crude product, which was prepared from (*S*)-**1b** (76.2 mg, 0.150 mmol), **4b**, and $Rh_2(esp)_2$ (5.69 mg, 0.00750 mmol) at 40 °C for 3 h (the first step) and at 0 °C for 3 h (the second step), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6bb** (66.2 mg, 65% yield) as a colorless oil.

*((2′R,4S,5S)-2′-{[(S)-tert-Butylsulfinyl]amino}-7-(methoxycarbonyl)-5-phenyl-2,3,5,8-tetrahydro-1H-spiro[azulene-4,1′-cyclopentane]-2,2-diyl)bis(methylene) Diacetate (**6cb**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31−7.23 (m, 3H), 7.12 (d, J = 7.0 Hz, 2H), 7.10 (d, J = 7.3 Hz, 1H), 4.06 (t, J = 7.3 Hz, 1H), 3.99 (d, J = 10.9 Hz, 1H), 3.96 (d, J = 10.9 Hz, 1H), 3.91 (d, J = 10.9 Hz, 1H), 3.76 (d, J = 10.9 Hz, 1H), 3.73 (s, 3H), 3.44 (d, J = 5.2 Hz, 1H), 3.29 (d, J = 21.0 Hz, 1H), 3.21 (d, J = 21.3 Hz, 1H), 2.98 (d, J = 9.1 Hz, 1H), 2.41−2.26 (m, 3H), 2.17 (d, J = 16.6 Hz, 1H), 2.06−2.01 (m, 7H), 1.88−1.81 (m, 2H), 1.74−1.70 (m, 1H), 1.64−1.57 (m, 2H), 1.18 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.0 (2C), 168.2, 141.5, 138.5, 136.1, 132.0, 130.3 (2C), 128.2 (2C), 128.0, 127.5, 67.1, 66.5, 64.5, 55.8, 55.8, 52.2, 49.2, 45.7, 44.7, 42.4, 32.0, 31.4, 30.0, 22.7 (3C), 20.9 (2C), 19.6. IR (neat) $\tilde{\nu}$: 3275, 3024, 2955, 2893, 2844, 1740, 1650, 1599 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{32}H_{43}NNaO_7S^+$ [(M + Na)$^+$] 608.2652, found 608.2659. $[\alpha]_D^{26}$: − 91.0 (c 4.91, $CHCl_3$).

According to the general procedure for one-pot synthesis of **6**, a crude product, which was prepared from (*S*)-**1c** (61.7 mg, 0.150 mmol), **4b**, and $Rh_2(piv)_4$ (4.58 mg, 0.00750 mmol) at 40 °C for 4 h

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(the first step) and at 0 °C for 3 h (the second step), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6cb** (77.4 mg, 88% yield) as a colorless oil.

According to the general procedure for one-pot synthesis of **6**, a crude product, which was prepared from (*S*)-**1c** (61.7 mg, 0.150 mmol), **4b**, and $Rh_2(esp)_2$ (5.69 mg, 0.00750 mmol) at 40 °C for 4 h (the first step) and at 0 °C for 3 h (the second step), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6cb** (70.6 mg, 80% yield) as a colorless oil.

*Methyl (1S,2R,5′S)-2-{[(S)-tert-Butylsulfinyl]amino}-5′-phenyl-1′,3′,5′,8′-tetrahydrodispiro[cyclopentane-1,4′-azulene-2′,9″-fluorene]-7′-carboxylate (**6db**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65−7.62 (m, 2H), 7.49 (d, J = 7.3 Hz, 1H), 7.40−7.20 (m, 11H), 3.91 (dd, J = 16.2, 7.1 Hz, 1H), 3.74−3.71 (m, 4H), 3.42 (app t, J = 23.6 Hz, 2H), 3.25 (d, J = 9.6 Hz, 1H), 3.12 (d, J = 16.9 Hz, 1H), 3.04 (d, J = 16.9 Hz, 1H), 2.88 (d, J = 16.6 Hz, 1H), 2.62 (d, J = 16.6 Hz, 1H), 2.28−2.27 (m, 1H), 1.94−1.93 (m, 1H), 1.79−1.77 (m, 1H), 1.70−1.60 (m, 3H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.1, 154.1 (2C), 142.9, 139.8, 139.4, 139.3, 136.1, 134.3, 130.4 (2C), 129.3, 128.4 (2C), 127.7. 127.7, 127.5, 127.2, 127.1, 122.7, 122.3, 119.8, 119.7, 66.5, 56.0, 55.4, 53.2, 53.1, 52.2, 52.1, 51.9, 33.7, 33.2, 30.5, 22.7 (3C), 20.5. IR (neat) $\tilde{\nu}$: 3299, 3063, 2956, 2839, 1710, 1659, 1600 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{38}H_{41}NNaO_3S^+$ [(M + Na)$^+$] 614.2699, found 614.2695. $[\alpha]_D^{27}$: − 14.4 (c 5.91, $CHCl_3$).

According to the general procedure for one-pot synthesis of **6**, a crude product, which was prepared from (*S*)-**1d** (62.6 mg, 0.150 mmol), **4b**, and $Rh_2(piv)_4$ (4.58 mg, 0.00750 mmol) at 40 °C for 4 h (the first step) and at 0 °C for 3 h (the second step), was purified by silica gel column chromatography (70:30 to 0:100 hexane/EtOAc) to give **6db** (65.4 mg, 74% yield) as a colorless oil.

According to the general procedure for one-pot synthesis of **6**, a crude product, which was prepared from (*S*)-**1d** (62.6 mg, 0.150 mmol), **4b**, and $Rh_2(esp)_2$ (5.69 mg, 0.00750 mmol) at 40 °C for 4 h (the first step) and at 0 °C for 3 h (the second step), was purified by silica gel column chromatography (70:30 to 0:100 hexane/EtOAc) to give **6db** (72.4 mg, 82% yield) as a colorless oil.

*Methyl (2′R,4S,5S)-2′-{[(S)-tert-Butylsulfinyl]amino}-5-phenyl-2-tosyl-2,3,5,8-tetrahydro-1H-spiro[cyclohepta[c]pyrrole-4,1′-cyclopentane]-7-carboxylate (**6eb**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 7.04−6.99 (m, 3H), 6.90 (d, J = 7.8 Hz, 2H), 4.14 (d, J = 14.6 Hz, 1H), 4.09 (d, J = 14.6 Hz, 1H), 4.04 (t, J = 7.4 Hz, 1H), 3.92 (d, J = 13.5 Hz, 1H), 3.70 (s, 3H), 3.40 (d, J = 13.0 Hz, 1H), 3.34 (d, J = 7.5 Hz, 1H), 3.20 (s, 2H), 2.86 (d, J = 8.6 Hz, 1H), 2.47 (s, 3H), 2.33−2.26 (m, 1H), 1.91−1.75 (m, 3H), 1.61 (dd, J = 13.4, 7.9 Hz, 1H), 1.43 (dt, J = 13.4, 10.4 Hz, 1H), 1.02 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.9, 143.4, 141.3, 138.1, 134.3, 134.0, 130.0 (2C), 129.8 (2C), 128.7, 128.4 (2C), 127.7 (2C), 127.4, 127.0, 64.2, 59.1, 58.9, 55.8, 55.4, 52.3, 49.0, 32.4, 30.4, 27.6, 22.5 (3C), 21.7, 19.6. IR (neat) $\tilde{\nu}$: 3276, 2954, 1711, 1650, 1598, 1344, 1162 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{32}H_{40}N_2NaO_5S_2^+$ [(M + Na)$^+$] 619.2271, found 619.2276. $[\alpha]_D^{26}$: − 112.2 (c 2.61, $CHCl_3$).

According to the general procedure for one-pot synthesis of **6**, a crude product, which was prepared from (*S*)-**1e** (63.4 mg, 0.150 mmol), **4b**, and $Rh_2(piv)_4$ (4.58 mg, 0.00750 mmol) at 40 °C for 13 h (the first step) and at 0 °C for 3 h (the second step), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6eb** (40.2 mg, 45% yield) as a colorless oil.

According to the general procedure for one-pot synthesis of **6**, a crude product, which was prepared from (*S*)-**1e** (63.4 mg, 0.150 mmol), **4b**, and $Rh_2(esp)_2$ (5.69 mg, 0.00750 mmol) at 40 °C for 13 h (the first step) and at 0 °C for 3 h (the second step), was purified by silica gel column chromatography (50:50 to 0:100 hexane/EtOAc) to give **6eb** (37.6 mg, 42% yield) as a colorless oil.

Chemical Transformation for X-ray Crystal Structure Analysis. A suspension of **6cb** (250 mg, 0.427 mmol) and K_2CO_3 (177 mg, 1.28 mmol) in MeOH (4.3 mL) was stirred at rt for 0.5 h. The mixture was diluted with EtOAc. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. The residue was used in the next reaction without purification. A solution of the crude diol, 2,2-dimethoxypropane (0.525 mL, 4.27 mmol), and PPTS (32.2 mg, 0.128 mmol) in acetone (2.2 mL) and CH_2Cl_2 (2.2 mL) was stirred at rt for 14 h. The reaction was quenched with saturated aq $NaHCO_3$ and the mixture extracted with EtOAc. The organic layer was washed with saturated aq $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was used in the next reaction without purification. A solution of the crude acetonide and 2 N aq NaOH (0.854 mL, 1.71 mmol) in THF (2.2 mL) and MeOH (2.2 mL) was stirred at rt for 14 h. The reaction was quenched with 2 N aq HCl (0.854 mL) and the mixture extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was used in the next reaction without purification. A solution of the crude acid, HATU (487 mg, 1.28 mmol), NH_4Cl (68.5 mg, 1.28 mmol), and iPr$_2$NEt (0.447 mL, 2.56 mmol) in DMF (4.3 mL) was stirred at rt for 14 h. The reaction was quenched with saturated aq $NaHCO_3$ and the mixture extracted with EtOAc. The organic layer was washed with saturated aq $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (100:0 to 95:5 $CHCl_3$/MeOH) to give **7** (124.3 mg, 55% yield in four steps) as a white solid. The structure and absolute configuration of **7** were unambiguously determined by X-ray crystal structure analysis.

*(1S,2R,5′S)-2-{[(S)-tert-Butylsulfinyl]amino}-2″,2″-dimethyl-5′-phenyl-1′,3′,5′,8′-tetrahydrodispiro[cyclopentane-1,4′-azulene-2′,5″-[1,3]dioxane]-7′-carboxamide (**7**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28−7.23 (m, 3H), 7.13 (d, J = 6.6 Hz, 2H), 6.54 (d, J = 7.6 Hz, 1H), 5.68 (br s, 2H), 4.10 (t, J = 7.2 Hz, 1H), 3.58−3.56 (m, 3H), 3.44 (d, J = 11.2 Hz, 1H), 3.39 (d, J = 7.1 Hz, 1H), 3.30−3.21 (m, 2H), 3.09 (d, J = 8.5 Hz, 1H), 2.52 (d, J = 16.8 Hz, 1H), 2.41 (d, J = 17.1 Hz, 1H), 2.32−2.25 (m, 1H), 2.15 (d, J = 16.8 Hz, 1H), 2.06−2.01 (m, 1H), 1.89−1.61 (m, 5H), 1.41 (s, 3H), 1.35 (s, 3H), 1.17 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 139.1, 136.0, 134.9, 132.2, 131.6, 130.4 (2C), 127.9 (2C), 127.3, 97.6, 69.6, 69.4, 64.4, 56.0, 55.8, 48.6, 47.3, 45.8, 38.1, 31.9, 31.1, 30.4, 24.4, 23.1, 22.8 (3C), 19.6. IR ($CHCl_3$) $\tilde{\nu}$: 3373, 3182, 2958, 2856, 1652, 1599 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{30}H_{42}N_2NaO_4S^+$ [(M + Na)$^+$] 549.2758, found 549.2758. $[\alpha]_D^{23}$: − 176.6 (c 1.00, $CHCl_3$). Mp: 187−188 °C (recrystallized from hexane/MeOAc at 0 °C).

CCDC 1442259 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01502.

Spectroscopic data (^{1}H and ^{13}C NMR) of new compounds (PDF)

Single-crystal X-ray crystallography data for product **7** (CIF)

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Notes

The authors declare no competing financial interest.

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