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Total Synthesis of (-)-Graminin A Based on Asymmetric Cyclization Carbonylation of Propargyl Acetate

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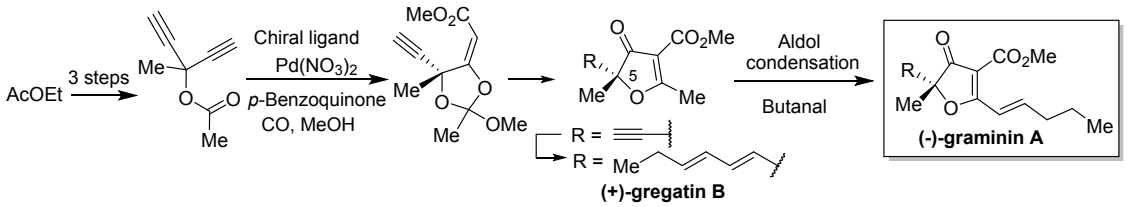
Supporting Information Placeholder



ABSTRACT: The first total synthesis of (-)-graminin A is described. Key features of our synthetic approach involve a palladium-catalyzed asymmetric cyclization carbonylation of prochiral propargylic acetate, conversion of the orthoester product into the methyl 4-oxo-3-furancarboxylate, and copper complex mediated aldol condensation of (+)-gregatin B bearing a diene moiety. A new synthesis of (+)-gregatin B and the first synthesis of (-)-graminin A were achieved.

INTRODUCTION

Methyl 4-oxo-3-furancarboxylates are important structural motifs, because they exist in a variety of natural products with unique biological activities.[1] Gregatins and aspertetronins were isolated from *Cephalosporium gregatum* and *Aspergillus rugulosus*, respectively.[2] The core structure of these compounds has been revised twice, with Burghart-Stoll and Brückner assigning the true structure based on total synthesis and NMR spectroscopic comparison to related compounds.[3] Graminin A was isolated as the main component from the culture filtrate of *Cephalosporium gramineum* (Figure 1).[4]

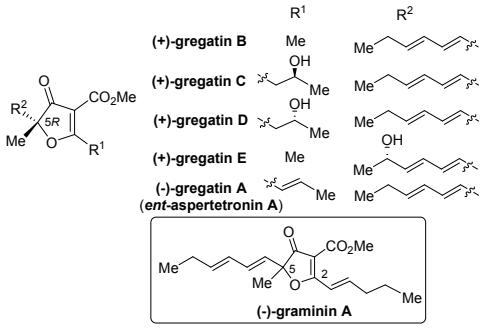
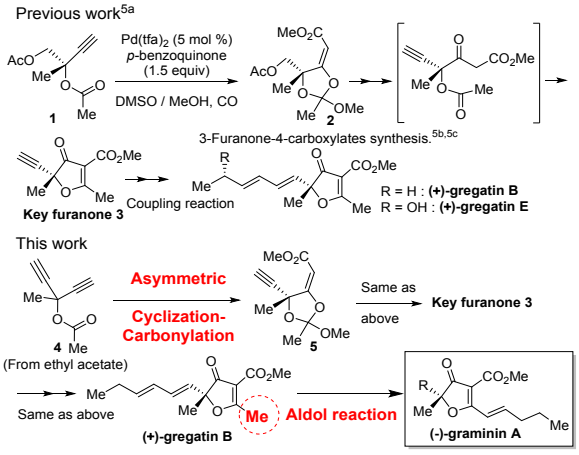


Figure 1. Gregatins A-E and Graminin A

Although the 2D structure was proposed as described above, the absolute configuration was not determined, and high resolution NMR data were not reported. Gregatins B-E having the 5*R* configuration exhibit dextro optical rotation. Interestingly, when the alkyl substituent on C2 (R^1) was changed to the alkene moiety (gregatin A), the sign of the optical rotation was reversed.

Scheme 1. Our previous work and this work



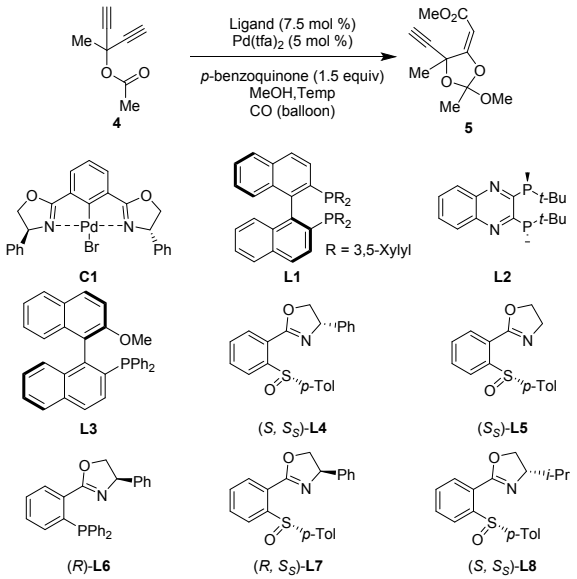
On the basis of the sign of the optical rotation and structural similarities, we assumed that the absolute configuration of C5 in (-)-graminin A to be *R*.

Previously, we reported the total synthesis of gregatins B and E based on palladium-catalyzed cyclization carbonylation of optically active propargyl acetate **1** (Scheme 1, previous work).[5a] The orthoester **2** was converted into the key furanone **3** by using our previously reported procedure.[5b] The previous synthesis had two disadvantages: 1) Seven steps were required to prepare the optically active propargyl acetate **1**. 2) Conversion of the acetoxymethyl group into an alkyne moiety was necessary. To improve the efficiency of the synthesis, we investigated a second generation route (Scheme 1, this work). Key features of this work involve a palladium-catalyzed asymmetric cyclization carbonylation of prochiral propargylic acetate **4** and Cu complex-mediated aldol reaction of (+)-gregatin B bearing a diene moiety.

RESULTS AND DISCUSSION

The prochiral propargylic acetate **4** was obtained from ethyl acetate via a three-step sequence. Thus, addition of TMS-acetylide followed by desilylation, and subsequent acetylation afforded **4** in 74% yield (three steps). Initially, we screened several kinds of mono- to tri-dentate ligands for the asymmetric cyclization carbonylation of prochiral propargylic acetate **4** (Table 1, entries 1-5).[6]

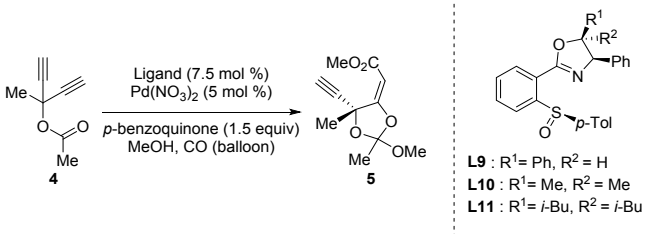
Table 1. Asymmetric cyclization carbonylation of 4: ligand screening and investigation of palladium counterion



Entry	Catalyst	Conditions	Yield [%] (dr)	ee (%)
1	**C1**	rt, 30h	60 (1.5/1)	0/0
2	Pd(tfa)$_2$/**L1**	rt, 18h	63 (1/1)	-43/26
3	Pd(tfa)$_2$/**L2**	0 °C ~ rt, 46 h	10 (1.5/1)	-43/-47
4	Pd(tfa)$_2$/**L3**	0 °C, 18 h	34 (1.6/1)	-42/-28
5	Pd(tfa)$_2$/**L4**	0 °C ~ rt, 69 h	27 (1.8/1)	-52/-55
6	Pd(tfa)$_2$/**L5**	0 °C, 48 h	18 (1.6/1)	-17/-31
7	Pd(tfa)$_2$/**L6**	0 °C, 25 h	27 (1.6/1)	55/54
8	Pd(tfa)$_2$/**L7**	-20 °C, 41 h	66 (1.2/1)	22/-24
9	Pd(tfa)$_2$/**L8**	0 °C, 23 h	49 (1.7/1)	-46/-40
10	$PdCl_2(CH_3CN)_2$/**L4**	0 °C ~ rt, 100 h	58 (1.5/1)	-25/-17
11	$Pd(BF_4)_2(CH_3CN)_4$/**L4**	0 °C, 46 h	56 (2/1)	-53/-51
12	Pd(NO$_3$)$_2$/**L4**	-10 °C, 84 h	62 (1.9/1)	-62/-59

Among them, sulfoxide-oxazoline (sox) ligand[7] **L4** gave moderate enantioselectivity (Table 1, entry 5). In the case of **L5** bearing an achiral oxazoline moiety, lower enantioselectivity resulted (Table 1, entry 6). The use of **L6** bearing chiral oxazoline and achiral phosphine moieties gave almost the same result as that using **L4** (Table 1, entries 5 and 7). These results suggested that the stereochemistry of the oxazoline plays an important role in chiral induction. Diastereomer **L7** and isopropyl oxazoline **L8** reduced the enantioselectivity (Table 1, entries 8 and 9). Next, we investigated the palladium counterion (Table 1, entries 10-12). The use of NO_3^- as a counterion resulted in improved yield and enantioselectivity (Table 1, entry 12).Finally, we investigated three kinds of sox ligands **L9-L11** bearing additional substituents at the C5 position of the oxazoline ring (Table 2, entries 1-4). Among them, 5,5-dimethyloxazoline **L10** improved the enantioselectivity, affording 72% ee of **5** in 65% yield (Table 2, entry 3). The absolute configuration and ee value were determined after conversion to the known key furanone **3**.

Table 2. Ligand tuning

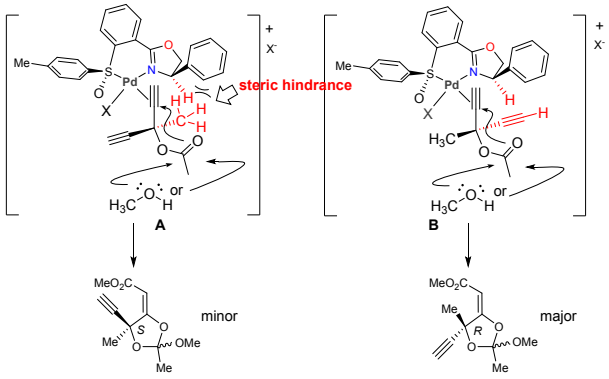


Entry	Ligand	Conditions	Yield (%)	ee (%)[a]
1	**L9**	-10 °C, 84 h	64	65
2	**L10**	-10 °C, 48 h	52	70
3	**L10**	-20 °C, 94 h	65	72
4	**L11**	-20 °C, 72 h	60	72

[a]Absolute configuration and ee value were determined after conversion to the furanone **3**.

A model for the observed stereochemical outcome of the cyclization carbonylation is proposed as shown in Scheme 2. Based on the results using **L4** and **L6** (Table 1, entries 5 and 7), the major coordination site of the substrate is assumed to be next to the oxazoline. The alkyne-coordinated complex **B** should be slightly favored over complex **A**, because the alkyne moiety has a linear or straight geometry, leading to the major enantiomer.

Scheme 2. Working model of the asymmetric cyclization carbonylation of 4



With the optimal conditions in hand, we investigated the concise synthesis of (+)-gregatin B (Scheme 3). Asymmetric cyclization carbonylation of **4** using the conditions of entry 3 in Table 2 gave the orthoester **5** in 65% yield. The orthoester was converted into the key furanone **3** according to our previously reported procedure.[5a,b] Thus, acid treatment of orthoester **5** followed by Knoevenagel-type condensation gave the key furanone **3** in 74% yield (two steps, 72% ee). The optical purity of **3** was enriched by recrystallization from CH_2Cl_2 / hexane (65% yield, 96% ee). Regioselective palladium-catalyzed hydrostannylation[8] of **3** followed by reaction with iodine afforded iodide (*R*)-**6** in 71% yield. Finally, (+)-gregatin B was obtained using the Suzuki-Miyaura coupling reaction in 80% yield.[5a]

Scheme 3. Concise total synthesis of (+)-gregatin B

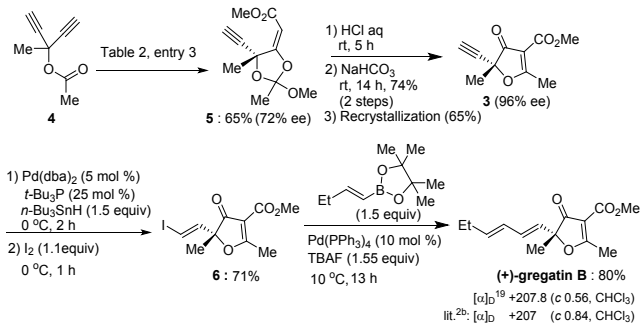
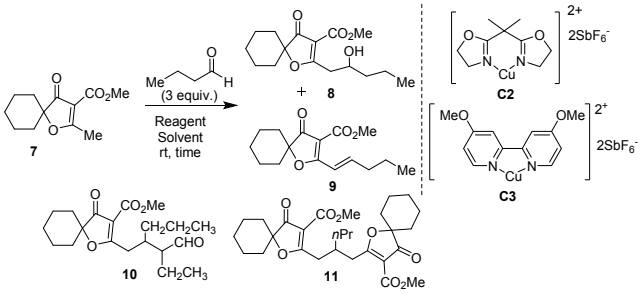


Table 3. Investigation of aldol reaction using model substrate 7



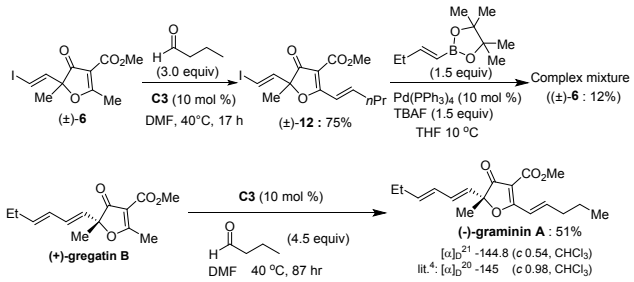
Entry	Reagent / Solvent	Time (h)	Yield of **8** (%)	Yield of **9** (%)
1[a]	Piperidine / AcOH (1:5) in CH_2Cl_2	23	-	5
2[b]	Piperidine / AcOH (1:5) in DMSO	0.2	-	15
3[c]	*t*BuOK (1.5 eq.) in THF	0.5	48	-
4[d]	K_2CO_3 (1.0 eq) in DMSO	2.0	-	-
5	**C2** (5 mol %) in DMF	72	-	53
6[e]	**C2** (5 mol %) in DMF	96	-	67
7[e]	**C3** (5 mol %) in DMF	74		83

[a] Recovery 94%. [b] **10** was obtained in 78% yield. [c] -20°C, **11** was obtained in 19% yield. [d] **11** was obtained in 70% yield. [e] [f] 40 °C.

Prior to the synthesis of graminin A, we investigated the vinylogous aldol reaction[9] of model substrate **7** with butanal (Table 3). Acidic conditions gave enone **9** (Table 3, entries 1 and 2), while basic conditions predominantly gave aldol adduct **8** (Table 3, entry 3). However, in both cases, **8** and **9** were obtained in low yields due to recovery of **7** (Table 3, entry 1) or over reactions (Table 3, entries 2-4). Over reaction products **10** and **11** should be produced by conjugate addition of butanal and **7** to the aldol condensation product **9**, respectively. Recently, [Cu(II)(box)]X_2 was reported as a useful catalyst for activation of β-ketoesters.[10] Inspired by these studies, box complex **C2** and bipyridine complex **C3** were tested in this reaction. The reaction of **7** with butanal in the presence of **C2** (5 mol %) in DMF afforded desired enone **9** in 53% yield (Table 3, entry 5). A higher reaction temperature increased the yield of **9**, and bipyridine complex **C3** gave a satisfactory yield (Table 3, entries 6 and 7). Mechanistically, the β-ketoester moiety was activated by the copper complex, which makes the methyl group more acidic. Thus, the vinylogous aldol reaction

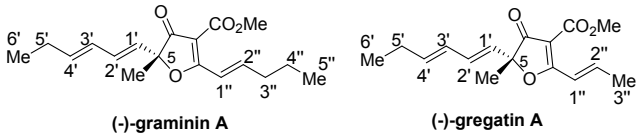
proceeded smoothly without base. We selected **C3** as suitable catalyst for the synthesis of (-)-graminin A.

Scheme 4. Synthesis of (-)-graminin A



(-)-Graminin A has two kinds of diene moieties. We investigated two routes for the construction of the second diene moiety (Scheme 4). In the first route, the vinylogous aldol condensation of iodo vinyl furanone (±)-**6** with butanal proceeded smoothly, affording (±)-**12** in 75% yield. Unfortunately, the conjugated diene moiety was unstable under basic conditions and the Suzuki-Miyaura coupling reaction of (±)-**12** gave a complex mixture, with only a small amount (12%) of (±)-**6** recovered by retro-aldol reaction. In the second route, we investigated the vinylogous aldol reaction of (+)-gregatin B with butanal using **C3** as a catalyst, and desired (-)-graminin A was obtained in 51% yield. As shown in Table 4 and Fig. 2, the ^{1}H NMR and ^{13}C NMR data for (-)-graminin A were almost identical to those for (-)-gregatin A[3b] except for signals corresponding to C3"-H to C5"-H and C3" to C5".

Table 4. ^{1}H NMR spectra of (-)-graminin A and (-)-gregatin A



Position	Proton	Synthetic (-)-graminin A (ppm)[a]	Natural gregatin A (ppm)[b]
6'	3H, *t*	0.99 or 1.00	0.96
5'	2H, *m*	2.06-2.13	2.06
4'	1H, *dt*	5.81	5.7-6.0 (*m*)
3'	1H, *dd*	5.98	
2'	1H, *dd*	6.27	6.24
1'	1H, *d*	5.57	5.54
C5-Me	3H, *s*	1.55	1.53
OMe	3H, *s*	3.84	3.83
1"	1H, *dt*	7.32	7.32 (*br-d*)
2"	1H, *dt*	7.19	7.18 (*dq*)
3"	2H, *q*	2.35	2.05 (3H, *dd*)
4"	2H, *sext*	1.59	-
5"	3H, *t*	0.99 or 1.00	-

[a]400 MHz, $CDCl_3$. [b]250 MHz, $CDCl_3$.

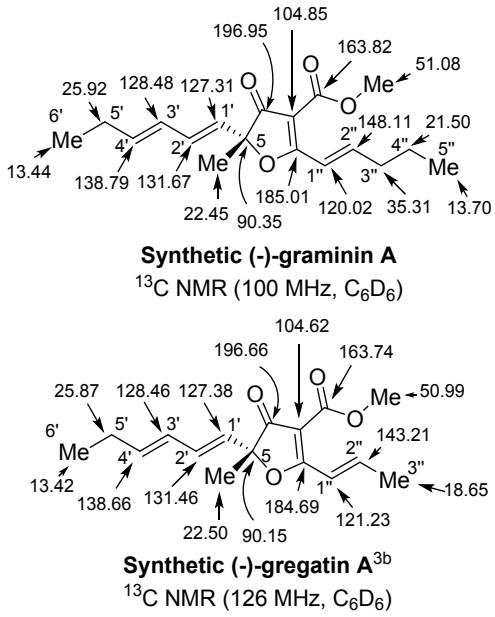


Figure 2. ^{13}C NMR of graminin A and gregatin A

CONCLUSIONS

A new total synthesis of (+)-gregatin B and the first total synthesis of (-)-graminin A have been achieved. The optically active furanone skeleton was effectively constructed based on Pd^{II}-catalyzed asymmetric cyclization carbonylation of prochiral propargyl acetate **4**, followed by ring conversion. The (*E*,*E*)-diene moiety was successfully prepared by the Suzuki-Miyaura coupling reaction. The vinylogous aldol condensation of (+)-gregatin B with butanal was achieved by using a cationic copper catalyst. This methodology would be applicable for the synthesis of related natural products such as graminin C,[10] aspertetronin A, gregatine A and penicilliol A.[11]

EXPERIMENTAL SECTION

General Information. All melting points were determined on a microscopic melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) using $CDCl_3$ or C_6D_6 as the solvent and TMS as the internal standard. In the case of DMSO-d_6, solvent peak was used as a reference (2.49 ppm for ^{1}H, and 39.5 ppm for ^{13}C). Coupling constants (*J*) are reported in Hertz (Hz), and spin multiplicities are represented by the following symbols: s (singlet), br-s (broad singlet), d (doublet), br-d (broad doublet), t (triplet), q (quartet), sext (sextet) and m (multiplet). High-resolution mass spectra were obtained using high-resolution EI (double focusing) or FAB (double focusing) or ESI-TOF mass spectrometers. Infrared spectra (IR) were recorded on a FT-IR spectrophotometer and are reported as wavelength numbers (cm^{-1}). Determination of enantiomeric excesses was performed by chiral HPLC analysis of noncrystallized samples. Column conditions are reported in the

experimental section below. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. Column chromatography was performed using silica gel (particle size 100-210 mm (regular), 40-50 mm (flash)).

3-Methylpenta-1,4-diyn-3-yl acetate (4). To a solution of trimethylsilylacetylene (4.13 g, 0.042 mol) in THF (50 mL) was added dropwise *n*-BuLi (15.5 mL, ca. 2.65 M in THF, 0.041 mol) at -40 °C under Ar. After the solution was stirred at -40 °C for 0.5 h, EtOAc (1.76 g, 0.020 mol) was added to the stirred solution via syringe at −40 °C. After stirring at the same temperature for 12 h, the mixture was diluted with saturated NH_4Cl (70 mL) and extracted with EtOAc (40 mL x 2). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. To a solution of the crude product in MeOH (30 mL) was added K_2CO_3 (2.76 g, 0.020 mol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The mixture was diluted with brine (50 mL) and extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the corresponding alcohol, which was dissolved in pyridine (6.33 g, 0.080 mol) and Ac_2O (6.13 g, 0.060 mol). To this solution was added 4-dimethylaminopyridine (24.4 mg, 0.20 mmol) at room temperature. After stirring at the same temperature for 27 h, the mixture was diluted with H_2O (80 mL) and extracted with EtOAc (80 mL x 2). The organic layer was washed with 2 M HCl (80 mL) and saturated $NaHCO_3$ (80 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc = 10/1) to afford acetate **4** (2.02 g, 74% yield, 3 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, s), 2.10 (3H, s), 2.65 (2H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 14.1, 30.4, 63.1, 72.9, 80.0, 168.3; IR (KBr): 3293, 3252, 3006, 1752, 1238 cm^{-1}; HRMS (EI) m/z: [M$^+$] calcd for $C_8H_8O_2$ 136.0524; found 136.0522.

Methyl (E)-2-(5-ethynyl-2-methoxy-2,5-dimethyl-1,3-dioxolan-4-ylidene)acetate (5) (Table 1). The reaction was performed according to the typical procedure for asymmetric cyclization carbonylation of **4**. The orthoester **5** was obtained as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$) diastereomer A : δ 1.68 (3H, s), 1.96 (3H, s), 2.66 (1H, s), 3.36 (3H, s), 3.71 (3H, s), 5.45 (1H, s); diastereomer B : δ 1.73 (3H, s), 2.03 (3H, s), 2.65 (1H, s), 3.30 (3H, s), 3.71 (3H, s), 5.44 (1H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$) diastereomer A : δ 24.7, 27.0, 50.1, 51.1, 73.3, 78.7, 80.8, 90.4, 124.1, 166.0, 168.8; diastereomer B : δ 24.0, 25.5, 49.4, 51.1, 73.2, 77.6, 81.4, 90.5, 124.3, 166.0, 168.2; IR (KBr): 2346, 2122, 1724, 1660, 1097 cm^{-1}; HRMS (EI) m/z: [M$^+$] calcd for $C_{11}H_{14}O_5$ 226.0841; found 226.0845; HPLC: Chiralcel OD-H, hexane/EtOH = 200/1, flow rate = 1.0 mL / min., diastereomer A: t_R = 8.6 min. (*S*), 48.0 min. (*R*); diastereomer B: t_R = 9.2 min. (*S*), 18.6 min. (*R*).

Typical procedure for asymmetric cyclization carbonylation of 4 (Table 2, Entry 3). To a 30-mL two-necked round-bottom flask containing a magnetic stirring bar, the substrate **4** (68.2 mg, 0.5 mmol), *p*-benzoquinone (81.8 mg, 0.75 mmol) and MeOH (7 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling via the three-way stopcock. A MeOH (1 mL) solution of $Pd(NO_3)_2$ (5.8 mg, 0.025 mmol) and **L10** (0.0375 mmol) was added to the stirred solution via syringe at −20 °C. The remaining catalyst was washed in MeOH (1 mL) twice and stirred for 94 h at the same temperature. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with 2 M NaOH (50 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL × 2) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/EtOAc (20/1) afforded the orthoester **5** (73.3 mg, 65%) as a colorless oil. (mixture of diastereomers, ratio = 2:1) Absolute configuration and ee value were determined after conversion to the furanone **3**.

Methyl (5R)-5-ethynyl-2,5-dimethyl-4-oxo-4,5-dihydrofuran-3-carboxylate (3). To a solution of **5** (79.6 mg, 0.352 mmol) in MeOH (3 mL) was added 2 M HCl (3 mL) at 0 °C. After stirring at room temperature for 1.0 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. To a solution of the crude product in MeOH (4 mL) was added $NaHCO_3$ (296 mg, 3.52 mmol), and the mixture was stirred at room temperature for 14 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel **(**hexane/EtOAc = 20/1**)** to afford furanone **3** (50.8 mg, 74% yield, 72% ee, 2 steps) as a white solid. Mp. 88-90°C; ^{1}H NMR ($CDCl_3$) δ 1.71 (3H, s), 2.65 (3H, s), 2.66 (1H, s), 3.85 (3H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 17.9, 23.9, 51.8, 76.1, 77.5, 82.8, 106.2, 162.8, 193.7, 196.1; IR (KBr): 3250, 2979, 2945, 2884, 2123, 1712, 1590 cm^{-1}; HRMS (EI) m/z: [M$^+$] calcd for $C_{10}H_{10}O_4$ 194.0579; found 194.0577; HPLC: Chiralcel OD-H, hexane/IPA = 15/1, flow rate = 0.5 mL / min., t_R = 23.2 min. (*R*), 26.5 min. (*S*). The optical purity of **3** (229.0 mg, 72%ee) was enriched by recrystallization from CH_2Cl_2 / hexane (148.0 mg, 65% yield, 96% ee). $[\alpha]^{20}_D$ +85.9 (*c* 0.60, $CHCl_3$).

Methyl (E)-(5R)-5-(2-iodovinyl)-2,5-dimethyl-4-oxo-4,5-dihydrofuran-3-carboxylate (6). $Pd(dba)_2$ (6.0 mg, 0.01 mmol) and *t*Bu_3P (25.7 μL, 1.0 M in toluene, 0.026 mmol) were added successively to CH_2Cl_2 (3 mL) and the resulting mixture was stirred at room temperature for 10 min under Ar. A solution of (*R*)-**3** (100 mg, 0.51 mmol) in CH_2Cl_2 (3 mL) was added, and the reaction mixture was cooled to 0 °C. A solution of Bu_3SnH (224.9 mg, 0.77 mmol) in CH_2Cl_2 (4 mL) was added dropwise at 0 °C via syringe over 15 min. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was concentrated and the residue was purified by column chromatography on 10% w/w anhydrous K_2CO_3-silica[12] (hexane/EtOAc = 70/1 to 5/1) to afford the vinylstannane (204.7 mg, 82% yield) as a colorless oil. $[\alpha]^{20}_D$ +88.3 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80-0.98 (15H, m), 1.24-1.52 (12H, m), 1.52 (3H, s), 2.66 (3H,s), 3.83 (3H, s), 5.90 (1H, d, $^2J_{Sn-H}$ = 59.6 Hz, J = 19.0 Hz), 6.35 (1H, d, $^3J_{Sn-H}$ = 61.0 Hz, J = 19.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 9.5, 13.7, 17.9, 22.2, 27.2, 28.9, 51.6, 93.2, 106.6, 131.1, 141.4, 163.5, 195.6, 197.7; IR (KBr): 2949, 2902, 2864, 2841, 1711, 1590, 1202 cm^{-1}; HRMS (ESI$^+$) m/z: [M+H]$^+$ calcd for $C_{22}H_{39}O_4Sn$ 487.1870; found: 487.1871.

To a mixture of the vinylstannane (285.2 mg, 0.588 mmol) in THF (2 mL) was added a THF (2 mL) solution of I_2 (164 mg,

0.647 mmol) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was diluted with EtOAc (20 mL) and washed with 10% $Na_2S_2O_3$ (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on 10% w/w anhydrous K_2CO_3-silica[12] (hexane/EtOAc = 4/1 to 3/1) to afford (+)**-6** (176 mg, 93% yield) as a white solid. Mp 136-138°C; $[\alpha]^{19}_D$ +107.0 (c 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.53 (3H, s), 2.65 (3H, s), 3.84 (3H, s), 6.56 (1H, d, *J* = 14.8 Hz), 6.66 (1H, d, *J* = 14.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 17.9, 22.1, 51.7, 79.7, 92.6, 106.9, 140.3, 162.9, 195.7, 196.0; IR (KBr): 1709, 1577, 1226, 1201, 1135, 954 cm^{-1}; HRMS (EI) m/z: [M+] calcd for $C_{10}H_{11}O_4I$ 321.9702; found 321.9704.

Synthesis of (+)-gregatin B. To a solution of (+)**-6** (64.4 mg, 0.2 mmol), boronate[3a] (56.2 mg, 0.309 mmol) and $Pd(PPh_3)_4$ (23.1 mg, 0.02 mmol) in THF (deoxygenated, 4 mL) was added dropwise TBAF (310 μL, 1.0 M in THF, 0.31 mmol) at 0 °C. After stirring at 10 °C for 13 h under Ar, the mixture was diluted with EtOAc (20 mL) and washed with sat. NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc = 4.5/1) to afford gregatin B (39.8 mg, 80% yield) as a pale yellow solid. The spectroscopic data was in agreement with that reported in the literature.[3b] $[\alpha]^{19}_D$ +207.8 (c 0.56, $CHCl_3$).

Aldol reaction using model substrate 7 (Table 3). *For entries 1 and 2* : To a solution of furanone **7** (100 mg, 0.45 mmol) and butylaldehyde (97 mg, 1.35 mmol) in solvent (5.0 mL) was added piperidine / AcOH = 1:5 (0.5 mL) at room temperature. After the solution was stirred for 0.2 ~ 23 h, the mixture was diluted with CH_2Cl_2 (40 mL) and washed with H_2O (2 x 40 mL). The aqueous layer was extracted with CH_2Cl_2 (40 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 15/1 to 10/1) to afford **9** and **10**.

Methyl (E)-4-oxo-2-(pent-1-en-1-yl)-1-oxaspiro[4.5]dec-2-ene-3-carboxylate (9). White solid; Mp 83-85°C; 15% yield, 19.0 mg (0.068 mmol); ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, t, *J* = 7.2 Hz), 1.35-1.82 (12H, m), 2.34 (2H, dq, *J* = 7.2, 1.6 Hz), 3.84 (3H, s), 7.14 (1H, dt, *J* = 15.8, 7.2 Hz), 7.32 (1H, dt, *J* = 15.8, 1.6 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 13.9, 21.5, 21.7 (2C), 24.4, 31.9 (2C), 35.5, 51.7, 91.2, 104.4, 119.6, 149.0, 163.9, 185.4, 200.8; IR (KBr): 2935, 2874, 1737, 1700, 1642, 1552, 1433, 1404, 1199, 1062, 981, 940, 822 cm^{-1}; HRMS (EI) m/z: [M$^+$] calcd for $C_{16}H_{22}O_4$ 278.1518; found 278.1517.

Methyl 2-(3-formyloctan-4-yl)-4-oxo-1-oxaspiro[4.5]dec-2-ene-3-carboxylate (10). Inseparable mixture of diastereomers (ratio = 7:3); colorless oil; 78% yield, 121.0 mg (0.346 mmol); ^{1}H NMR ($CDCl_3$) δ 0.86-0.92 (3H, m), 0.95 (3H, t, *J* = 7.4 Hz), 1.25-1.83 (17H, m), 2.47 (1H, br-s), 3.05 (0.6H, dd, *J* = 6.4, 5.2 Hz), 3.10 (1.4H, d, *J* = 7.4 Hz), 3.83 (3H, s), 9.71 (0.7H, d, *J* = 2.4 Hz), 9.74 (0.3H, d, *J* = 2.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) major diastereomer: δ 12.5, 14.1, 18.2, 20.1, 21.4 (2C), 24.2, 31.6 (2C), 33.0, 33.3, 36.3, 51.7, 56.2, 92.2, 107.7, 163.4, 197.2, 200.4, 204.5; mimor diastereomer: δ 12.5, 14.0, 18.3, 20.3, 21.4 (2C), 24.2, 31.8 (2C), 32.6, 33.6, 31.6, 51.7, 56.0, 92.3, 107.7, 163.4, 197.2, 200.3, 204.4; IR (KBr): 2939, 2867, 2712, 1711, 1585, 1443, 1393, 1200, 1111, 1056 cm^{-1}; HRMS (EI) m/z: [M$^+$] calcd for $C_{20}H_{30}O_5$ 350.2093; found 350.2092.

For entries 3 and 4: To a solution of furanone **7** (45 mg, 0.20 mmol) and butylaldehyde (43.3 mg, 0.60 mmol) in solvent (1.5 mL) was added *t*BuOK (33.7 mg, 0.30 mmol) or K_2CO_3 (27.6 mg, 0.20 mmol) at -20 °C or room temperature under Ar. After the solution was stirred for 0.5 ~ 2.0 h, the mixture was diluted with sat. NH_4Cl aq. (15 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (15 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 4/1 to 2/1) to afford **8** and **11**.

Methyl 2-(2-hydroxypentyl)-4-oxo-1-oxaspiro[4.5]dec-2-ene-3-carboxylate (8). Colorless oil; 48% yield, 28.2 mg (0.095 mmol); ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, *J* = 7.2 Hz), 1.37-1.87 (14H, m), 2.65 (1H, br-s), 3.13-3.23 (2H, m), 3.84 (3H, s), 4.10 (1H, br-s); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 14.0, 18.7, 21.4, 21.4, 24.3, 31.6, 31.7, 38.7, 40.0, 51.9, 69.9, 92.5, 108.2, 164.6, 196.1, 200.1; IR (KBr): 3459, 2935, 2864, 1704, 1579, 1440, 1391, 1202, 1113, 1057 cm^{-1}; HRMS (EI) m/z: [M$^+$] calcd for $C_{16}H_{24}O_5$ 296.1624; found 296.1623.

Dimethyl 2,2'-(2-propylpropane-1,3-diyl)bis(4-oxo-1-oxaspiro[4.5]dec-2-ene-3-carboxylate) (11). Yellow oil; 70% yield, 35.0 mg (0.07 mmol); ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, *J* = 7.2 Hz), 1.38-1.81 (24H, m), 2.57-2.60 (1H, m), 3.08 (2H, dd, *J* = 14.0, 6.4 Hz), 3.18 (2H, dd, *J* = 14.0, 7.2 Hz), 3.82 (6H, s); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 14.7, 19.4, 21.5, 24.3, 31.7, 34.9, 36.0, 51.6, 92.3, 107.9, 163.4, 196.7, 200.3; IR (KBr): 2934, 2860, 1705, 1583, 1439, 1390, 1198, 1111, 1056 cm^{-1}; HRMS (FAB) m/z: [M+H]$^+$ calcd for $C_{28}H_{39}O_8$ 503.2645; found 503.2644.

For entries 5 – 7 : The reaction was performed according to the synthesis of **(±)-12** using furanone **7** (45 mg, 0.20 mmol), butylaldehyde (43.3 mg, 0.60 mmol) and DMF (1.5 mL) afforded **9** in 83% yield, 41.7 mg (0.15 mmol), (Entry 7).

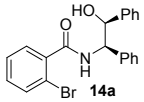
Methyl 5-((E)-2-iodovinyl)-5-methyl-4-oxo-2-((E)-pent-1-en-1-yl)-4,5-dihydrofuran-3-carboxylate ((±)-12). To a solution of (±)**-6** (25.0 mg, 0.078 mmol) and **C3** (5.8 mg, 0.0078 mmol) in DMF (1.0 mL) was added butylaldehyde (16.8 mg, 0.23 mmol) at room temperature. After the solution was stirred at 40 °C for 17 h, the mixture was diluted with EtOAc (20 mL) and washed with H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 25/1 to 20/1) to afford (±)**-12** (21.8 mg, 75% yield) as a yellow solid. Mp 68-72°C; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, t, *J* = 7.4 Hz), 1.55 (3H, s), 1.56-1.62 (2H, m), 2.36 (2H, q, *J* = 6.8 Hz), 3.85 (3H, s), 6.58 (2H, m), 7.19 (1H, dt, *J* = 16.0, 6.8 Hz), 7.30 (1H, dd, *J* = 16.0, 0.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 13.8, 21.3, 22.2, 35.6, 51.7, 79.3, 91.7, 103.8, 119.1, 140.9, 150.3, 163.1, 185.4, 196.4; IR (KBr): 2955, 2874, 1704, 1642, 1554, 1446, 1398, 1200, 1059 cm^{-1}; HRMS (EI) m/z: [M$^+$] calcd for $C_{14}H_{17}IO_4$ 376.0172; found 376.0173.

Suzuki-Miyaura coupling reaction of (±)-12. To a solution of (±)**-12** (20.0 mg, 0.054 mmol), boronate[3a] (29.5 mg, 0.080 mmol) and $Pd(PPh_3)_4$ (6.3 mg, 5.4 μmol) in THF (deoxygenated, 2.5 mL) was added dropwise TBAF (80 μL, 1.0 M in THF, 0.080 mmol) at 0 °C. After stirring at 0 °C for 22 h under Ar, the mixture was diluted with EtOAc (20 mL) and washed with

sat. NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/acetone = 15/1 to 5/1) to afford (±)-**6** (2.0 mg, 15% yield) along with a complex mixture.

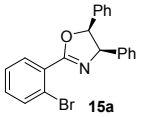
Synthesis of (-)-graminin A. To a solution of (+)-gregatin B (37.5 mg, 0.15 mmol) and **C3** (5.6 mg, 0.0075 mmol) in DMF (1.5 mL) was added butylaldehyde (16.2 mg, 0.23 mmol) at room temperature. After the solution was stirred at 40 °C for 17 h, **C3** (5.6 mg, 0.0075 mmol), butylaldehyde (16.2 mg, 0.23 mmol) and DMF (0.5 mL) were again added, and additional butylaldehyde (16.2 mg, 0.23 mmol) was added 46 h later. After stirring at 40 °C for 24 h, the reaction mixture was purified by flash chromatography on silica gel (hexane/AcOEt = 97/3 to 72/28) to afford graminin A (23.1 mg, 51% yield) as a colorless oil.TLC: hexane/EtOAc = 6/1 (R_f = 0.23); $[\alpha]^{21}_D$ -144.8 (c 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.99 (3H, t, *J* = 7.6 Hz), 1.00 (3H, t, *J* = 7.6 Hz), 1.55 (3H, s), 1.59 (2H, sext, *J* = 7.6 Hz), 2.06-2.13 (2H, m), 2.35 (2H, dq, *J* = 7.2, 1.2 Hz), 3.84 (3H, s), 5.57 (1H, d, *J* = 15.6 Hz), 5.81 (1H, dt, *J* = 15.2, 6.8 Hz), 5.98 (1H, dd, *J* = 15.2, 10.4 Hz), 6.27 (1H, dd, *J* = 15.6, 10.4 Hz), 7.19 (1H, dt , *J* = 15.6, 6.8 Hz), 7.32 (1H, dt, *J* = 15.6, 1.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 13.3, 13.8, 21.4, 22.5, 25.7, 35.5, 51.6, 90.5, 103.8, 119.4, 126.2, 127.8, 131.6, 139.3, 149.6, 163.5, 185.4, 198.4; ^1H NMR (C_6D_6) δ 0.68 (3H, t, *J* = 7.2 Hz), 0.82 (3H, t, *J* = 7.2 Hz), 1.12-1.22 (2H, m), 1.41 (3H, s), 1.79-1.89 (4H, m), 3.56 (3H, s), 5.51 (1H, dt, *J* = 15.2, 6.4 Hz), 5.57 (1H, d, *J* = 15.2 Hz), 5.83 (1H, dd, *J* = 15.2, 10.8 Hz), 6.42 (1H, dd, *J* = 15.2, 10.8 Hz), 6.96 (1H, dt, *J* = 16.0, 6.8 Hz), 7.59-7.63 (1H, dt, *J* = 16.0, 1.6 Hz); $^{13}C\{^1H\}$ NMR (C_6D_6) δ 13.4, 13.7, 21.5, 22.5, 25.9, 35.3, 51.1, 90.4, 104.9, 120.0, 127.3, 128.5, 131.7, 138.8, 148.1, 163.8, 185.0, 197.0; IR (KBr): 1711, 1642, 1554, 1397, 1202, 1052, 989 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ calcd for $C_{18}H_{25}O_4$ 305.1753; found 305.1726.

Preparation of ligand L9. [14]



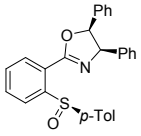
14a

Synthesis of 2-bromo-N-((1R,2S)-2-hydroxy-1,2-diphenylethyl)benzamide (14a). To a solution of (1*S*, 2*R*)-(+)-2-amino-1,2-diphenylethanol (**13a**) (1.20 g, 5.62 mmol) and Et_3N (1.13 g, 11.20 mmol) in CH_2Cl_2 (dehydrated, 20 mL) was slowly added a CH_2Cl_2 (10 mL) solution of 2-bromobenzoyl chloride (1.23 g, 5.62 mmol) at 0ºC under Ar. After stirring for 12 h at room temperature, the reaction mixture was quenched with water (140 mL) and extracted with CH_2Cl_2/MeOH = 8/1 (70 mL) three times. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The solid was washed with hexane/Et_2O = 1/5 to give **14a** (2.22 g, 100%) as a white solid. Mp 215-218°C; $[\alpha]^{26}_D$ -12.4 (c 0.47, DMSO); ^1H NMR (DMSO-d_6) δ 4.77 (1H, dd, *J* = 8.4, 5.2 Hz), 5.15 (1H, t, *J* = 9.0 Hz), 5.44 (1H, d, *J* = 5.6 Hz), 6.79 (1H, dd, *J* = 7.4, 1.8 Hz), 7.22-7.36 (8H, m), 7.40-7.45 (4H, m), 7.56 (1H, dd, *J* = 7.6, 1.2 Hz), 8.81 (1H, d, *J* = 9.2 Hz); $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ 58.5, 75.1, 118.8, 126.7, 127.1, 127.2 (2C), 127.3, 127.6 (2C), 127.7 (2C), 128.3 (2C), 128.4, 130.7, 132.6, 139.1, 140.9, 143.4, 165.7; IR (KBr): 3303, 1645, 1535, 1323, 1027, 750, 700 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ calcd for $C_{21}H_{19}BrNO_2$ 396.0599; found 396.0598.



15a

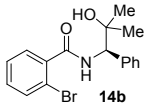
Synthesis of (4R,5S)-2-(2-bromophenyl)-4,5-diphenyl-4,5-dihydrooxazole (15a). **14a** (1.52 g, 3.84 mmol) dissolved in toluene (150 mL) was refluxed in a Dean–Stark apparatus with $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (474 mg, 0.384 mmol) for 48 h. The reaction mixture was cooled to room temperature and quenched with sat.$NaHCO_3$ (150 mL) and extracted with EtOAc (100 mL) twice. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 5/1) to give **15a** (0.90 g, 62%) as a white solid. Mp 97-99°C; $[\alpha]^{27}_D$ 144.3 (c 0.51, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.78 (1H, d, *J* = 10.2 Hz), 6.05 (1H, d, *J* = 10.2 Hz), 7.00-7.10 (10H, m), 7.34 (1H, dt, *J* = 8.0, 1.6 Hz), 7.42 (1H, dt, *J* = 7.6, 1.2 Hz), 7.73 (1H, dd, *J* = 8.0, 1.2 Hz), 7.95 (1H, dd, *J* = 7.6, 1.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 74.8, 85.8, 122.2, 126.7 (2C), 127.1, 127.4, 127.6, 127.8 (2C), 127.8 (2C), 128.0 (2C), 129.5, 131.9, 132.1, 134.3, 136.3, 137.5, 164.4; IR (KBr): 1654, 1463, 1325, 1087, 1023, 952, 733, 699 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ calcd for $C_{21}H_{17}BrNO$ 378.0494; found 378.0492.



L9

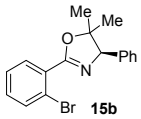
Synthesis of (4R,5S)-4,5-diphenyl-2-(2-((R)-p-tolylsulfinyl)phenyl)-4,5-dihydrooxazole (L9). To a solution of **15a** (1.00 g, 2.64 mmol) in Et_2O (20 mL) was slowly added *n*-BuLi (2.6 M in hexane, 1.22 mL, 3.17 mmol) at –78 °C under Ar atmosphere. After stirring at –78 °C for 0.5 h, a solution of (1*S*,2*R*,5*S*)-(+)-menthyl (*R*)- *p*-toluenesulfinate (0.93 g, 3.17 mmol) in Et_2O (10 mL) was added dropwise, stirred at –78 °C for 0.5 h, then room temperature for 4 h. To the mixture was added sat. NH_4Cl (40 mL) and extracted with EtOAc (30 mL) twice. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 3/1) to give **L9** (0.82 g, 72%) as white solid. Mp 80-83°C; $[\alpha]^{25}_D$ 225.6 (c 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.30 (3H, s), 5.77 (1H, d, *J* = 10.4 Hz), 5.92 (1H, d, *J* = 10.4 Hz), 6.56-6.58 (2H, m), 6.88-7.05 (10H, m), 7.49-7.52 (2H, m), 7.62 (1H, dt, *J* = 7.2, 1.2 Hz), 7.84 (1H, dt, *J* = 8.0, 1.2 Hz), 8.19 (1H, dd, *J* = 7.2, 1.2 Hz), 8.52 (1H, d, *J* = 8.0, 1.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 21.4, 75.0, 85.1, 124.8, 125.5, 126.3 (2C), 126.9 (2C), 127.0, 127.4 (2C), 127.5, 127.7 (2C), 127.9 (2C), 129.6 (2C), 130.1, 130.4, 132.3, 136.1, 136.9, 140.9, 143.5, 146.8, 162.0 IR (KBr): 3031, 1646, 1452, 1327, 1087, 1027, 962, 811, 732, 696 cm^{-1}; HRMS (EI) m/z: $[M^+]$ calcd for $C_{28}H_{23}NO_2S$ 437.1449; found 437.1450.

Preparation of ligand L10. [14]



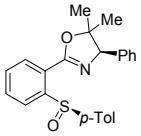
14b

Synthesis of (R)-2-Bromo-N-(2-hydroxy-2-methyl-1-phenylpropyl)benzamide (14b). To a solution of (*R*)-1-amino-2-methyl-1-phenylpropan-2-ol (**13b**) [13a] (603 mg, 3.65 mmol) and Et_3N (1.10 g, 10.87 mmol) in CH_2Cl_2 (dehydrated, 12 mL) was slowly added a CH_2Cl_2 (3 mL) solution of 2-bromobenzoyl chloride (794 mg, 3.62 mmol) at 0ºC under Ar. After stirring for 12 h at room temperature, the reaction mixture was quenched with water (30 mL) and extracted with CH_2Cl_2 (30 mL) three times. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane / EtOAc = 92/8 to 34/66) afforded **14b** (1.22 g, 96%) as a white solid. TLC: hexane/EtOAc = 2/1 (R_f = 0.16); Mp 118-120°C; $[\alpha]^{26}_D$ 23.2 (c 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.09 (3H, s), 1.43 (3H, s), 1.92 (1H, br-s), 5.02 (1H, d, *J* = 8.8 Hz), 7.15 (1H, d, *J* = 8.0 Hz), 7.23-7.40 (7H, m), 7.46 (1H, dt, *J* = 7.6, 1.6 Hz), 7.57 (1H, dd, *J* = 8.0, 0.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 27.9, 27.9, 62.0, 72.8, 119.2, 127.5, 127.7, 128.2 (2C), 128.3 (2C), 129.7, 131.2, 133.4, 137.7, 138.9, 167.0; IR (KBr): 3414, 3352, 1633, 1529, 1463, 1368, 1200, 1154, 742 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ calcd for $C_{17}H_{19}BrNO_2$ 348.0599; found 348.0599.



15b

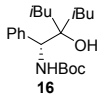
Synthesis of (R)-2-(2-bromophenyl)-5,5-dimethyl-4-phenyl-4,5-dihydrooxazole (15b). **15b** (1.20 g, 3.45 mmol) dissolved in xylene (150 mL) was refluxed in a Dean–Stark apparatus with tetraisopropyl orthotitanate (98 mg, 0.345 mmol) for 17h. The reaction mixture was cooled to room temperature and quenched with sat.$NaHCO_3$ (150 mL) and extracted with EtOAc (100 mL) twice. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane / EtOAc = 98/2 to 82/18) afforded **15b** (1.07 g, 94%) as a white solid. TLC: hexane/EtOAc = 10/1 (R_f = 0.19); Mp 84-85°C; $[\alpha]^{26}_D$ -10.5 (c 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, s), 1.70 (3H, s), 5.09 (1H, s), 7.27-7.40(7H, m), 7.67 (1H, dd, *J* = 8.0, 1.2 Hz), 7.77 (1H, dd, *J* = 7.6, 1.6 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 23.8, 29.1, 78.7, 88.2, 121.9, 127.1, 127.3 (2C), 127.5, 128.3 (2C), 130.4, 131.4, 131.6, 133.9, 138.6, 163.4; IR (KBr): 2974, 2874, 1665, 1465, 1334, 1246, 1086, 1032, 751 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ calcd for $C_{17}H_{17}BrNO$ 330.0494; found 330.0493.



L10

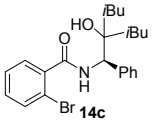
Synthesis of (R)-5,5-dimethyl-4-phenyl-2-(2-((R)-p-tolylsulfinyl)phenyl)-4,5-dihydrooxazole (L10). To a solution of **15b** (1.05 g, 3.18 mmol) in Et_2O (15 mL) was slowly added *n*-BuLi (2.6 M in hexane, 1.47 mL, 3.82 mmol) at –78 °C under Ar atmosphere. After stirring at –78 °C for 0.5 h, a solution of (1*S*,2*R*,5*S*)-(+)-menthyl (*R*)- *p*-toluenesulfinate (1.10 g, 3.82 mmol) in Et_2O (10 mL) was added dropwise, stirred at –78 °C for 0.5 h, then room temperature for 4 h. To the mixture was added sat. NH_4Cl (40 mL) and extracted with EtOAc (30 mL) twice. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane / acetone = 7/1 to 6.5/1) afforded **L10** (0.83 g, 67%) as a white solid. TLC: hexane/EtOAc = 3/1 (R_f = 0.20); Mp 96-97°C; $[\alpha]^{26}_D$ 100.2 (c 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, s), 1.62 (3H,s), 2.34 (3H, s), 5.08 (1H, s), 6.87-6.90 (2H, m), 7.08-7.10 (2H, m), 7.19-7.26 (3H, m), 7.2-7.55 (2H, m), 7.57 (1H, dt, *J* = 7.6, 1.2 Hz), 7.77 (1H, dt, *J* = 7.6, 1.2 Hz), 8.01 (1H, dd, *J* = 7.6, 1.2 Hz), 8.44 (1H, dd, *J* = 8.0, 1.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 21.3, 23.8, 28.7, 79.0, 87.8, 125.4, 125.8, 126.9 (2C), 127.2 (2C), 127.4, 128.0 (2C), 129.5 (2C), 129.7, 130.3, 132.0, 138.1, 140.7, 143.7, 146.3, 160.8; IR (KBr): 3526, 3464, 2981, 2869, 1641, 1456, 1335, 1083, 1017, 746 cm^{-1}; HRMS (EI) m/z: $[M^+]$ calcd for $C_{24}H_{23}NO_2S$ 389.1449; found 389.1449.

Preparation of ligand L11. [14]



16

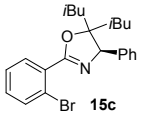
Synthesis of tert-butyl (R)-(2-hydroxy-2-isobutyl-4-methyl-1-phenylpentyl)carbamate (16). **16** was prepared according to the reported procedure.[13b] To a solution of (*R*)-*tert*-butoxycarbonylaminophenylacetic acid methyl ester[13a] (1.0 g, 4.25 mmol) in THF (dehydrated, 20 mL) was added $LaCl_3$·2LiCl (0.6 M in THF, 21.0 mL, 12.6 mmol) at room temperature under Ar. After stirring for 2 h at room temperature, the reaction mixture was added ^{t}BuMgBr (1.0 M in THF, 12.8 mL, 12.8 mmol) at 0°C, then stirred for 18 h at 0°C ~ rt. To the mixture was added sat. NH_4Cl (100 mL) and extracted with EtOAc (100 mL) twice. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane / EtOAc = 96/4 to 68/32) afforded **16** (1.24 g, 83%) as a white solid. TLC: hexane/EtOAc = 5/1 (R_f = 0.30); Mp 112-114°C; $[\alpha]^{25}_D$ 1.3 (c 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.4 Hz), 0.88-0.93 (1H, m), 0.99 (6H, d, *J* = 6.4 Hz), 1.24-1.78 (15H, m), 4.58 (1H, d, *J* = 9.2 Hz), 5.58 (1H, d, *J* = 8.4 Hz), 7.24-7.34 (5H, m); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 23.8, 24.1, 24.3, 24.9, 25.0 (2C), 28.4 (3C), 44.0, 46.0, 60.6, 77.7, 79.3, 127.3, 128.2 (2C), 128.4 (2C), 140.0, 155.3; IR (KBr): 3449, 3411, 2953, 2870, 1670, 1522, 1362, 1254, 1169, 875 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ calcd for $C_{21}H_{36}NO_3$ 350.2695; found 350.2695.



14c

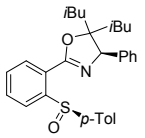
Synthesis of (R)-2-bromo-N-(2-hydroxy-2-isobutyl-4-methyl-1-phenylpentyl)benzamide (14c). To a solution of **16** (1.19 g, 3.41 mmol) in CH_2Cl_2 (6 mL) was added TFA (6 mL) at 0ºC, and the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo, the residue was diluted with CH_2Cl_2 (40 mL) and washed with 2M NaOH

(60 mL). The aqueous phase was extracted with CH_2Cl_2 (40 mL) twice and the combined organiclayers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude aminoalcohol **13c** was used without further purification. To a solution of **13c** and Et_3N (1.03 g, 10.22 mmol) in CH_2Cl_2 (dehydrated, 12 mL) was slowly added a CH_2Cl_2 (3 mL) solution of 2-bromobenzoyl chloride (748 mg, 3.41 mmol) at 0ºC under Ar. After stirring for 12 h at room temperature, the reaction mixture was quenched with water (30 mL) and extracted with CH_2Cl_2 (30 mL) three times. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (hexane/EtOAc = 94/6 to 51/49) to give **14c** (1.47 g, 100%, 2 steps) as white solid. TLC: hexane/EtOAc = 3/1 (R_f = 0.30); Mp 98-99°C; $[\alpha]^{25}_D$ -2.6 (c 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, d, *J* = 6.8 Hz), 0.87 (3H, d, *J* = 6.4 Hz), 0.92-0.98 (1H, m), 1.02 (3H, d, *J* = 6.8 Hz), 1.03 (3H, d, *J* = 6.4 Hz), 1.43-1.48 (2H, m), 1.64-1.89 (4H, m), 5.07 (1H, d, *J* = 8.8 Hz), 7.18 (1H, d, *J* = 8.4 Hz), 7.23-7.42 (7H, m), 7.46 (1H, dd, *J* = 7.6, 2.0 Hz), 7.57 (1H, dd, *J* = 7.8, 1.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 23.7, 24.1, 24.2, 24.2, 25.0, 25.0, 44.2, 46.2, 60.0, 77.7, 119.2, 127.5, 127.6, 128.3 (2C), 128.7 (2C), 129.8, 131.2, 133.4, 137.8, 139.1, 166.4; IR (KBr): 3403, 3300, 2952, 1631, 1537, 1462, 1153, 1032, 745, 701 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ calcd for $C_{23}H_{31}BrNO_2$ 432.1538; found 432.1538.



15c

Synthesis of (R)-2-(2-bromophenyl)-5,5-diisobutyl-4-phenyl-4,5-dihydrooxazole (15c). **14c** (1.40 g, 3.24 mmol) dissolved in xylene (150 mL) was refluxed in a Dean–Stark apparatus with tetraisopropyl orthotitanate (92 mg, 0.324 mmol). After stirring for 27 h at reflux temperature, tetraisopropyl orthotitanate (92 mg, 0.324 mmol) was again added, and additional tetraisopropyl orthotitanate (276 mg, 0.972 mmol) was added 24 h later. After stirring at same temperature for 17 h, the reaction mixture was cooled to room temperature and quenched with sat.$NaHCO_3$ (150 mL) and extracted with EtOAc (100 mL) twice. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (hexane/EtOAc = 98/2 to 82/18) to give **15c** (1.09 g, 81%) as yellow oil. TLC: hexane/EtOAc=10/1 (R_f = 0.45); $[\alpha]^{25}_D$ 27.2 (c 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.71 (3H, d, *J* = 6.8 Hz), 0.76 (3H, d, *J* = 6.4 Hz), 1.01-1.20 (8H, m), 1.69-1.78 (2H, m), 1.94-2.09 (2H, m), 5.03 (1H, s), 7.25-7.39 (7H, m), 7.68 (1H, d, *J* = 7.8, 1.0 Hz), 7.77 (1H, d, *J* = 7.6, 2.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 23.7, 24.2, 24.3, 24.7, 25.1, 25.1, 44.3, 47.0, 77.5, 92.6, 122.0, 127.2, 127.4, 128.1 (2C), 128.2 (2C), 130.5, 131.4, 131.6, 134.1, 138.7, 163.4; IR (KBr): 2954, 1658, 1465, 1331, 1097, 740, 693 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ calcd for $C_{23}H_{29}BrNO$ 414.1433; found 414.1433.



L11

Synthesis of (R)-5,5-diisobutyl-4-phenyl-2-(2-((R)-p-tolylsulfinyl)phenyl)-4,5-dihydrooxazole (L11). To a solution of **15c** (1.00 g, 2.41 mmol) in Et_2O (15 mL) was slowly added *n*-BuLi (2.6 M in hexane, 1.12 mL, 2.90 mmol) at –78 °C under Ar atmosphere. After stirring at –78 °C for 0.5 h, a solution of (1*S*,2*R*,5*S*)-(+)-menthyl (*R*)- *p*-toluenesulfinate (0.85 g, 2.90 mmol) in Et_2O (10 mL) was added dropwise, stirred at –78 °C for 0.5 h, then room temperature for 3 h. To the mixture was added sat. NH_4Cl (40 mL) and extracted with EtOAc (30 mL) twice. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (hexane/EtOAc = 95/5 to 60/40) to give **L11** (0.49 g, 43%) as pale yellow solid. TLC: hexane/EtOAc = 4/1 (R_f = 0.21); Mp 102-105°C; $[\alpha]^{26}_D$ 86.7 (c 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.68 (3H, d, *J* = 6.8 Hz), 0.75 (3H, d, *J* = 6.8 Hz), 0.90-1.05 (8H, m), 1.60-1.71 (2H, m), 1.88-2.03 (2H, m), 2.33 (3H, s), 5.29 (1H, s), 6.78-6.80 (2H, m), 7.06 (2H, d, *J* = 8.0 Hz), 7.16 (2H, t, *J* = 8.0 Hz), 7.21-7.25 (1H, m), 7.50-7.53 (2H, m), 7.57 (1H, dt, *J* = 7.6, 1.2 Hz), 7.78 (1H, dt, *J* = 7.6, 1.2 Hz), 7.96 (1H, dd, *J* = 7.8, 1.0 Hz), 8.47 (1H, dd, *J* = 8.0, 1.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 21.3, 23.6, 24.0, 24.1, 24.4, 24.8, 24.9, 44.1, 46.8, 77.9, 91.8, 124.9, 125.6, 125.8, 127.0 (2C), 127.2, 127.8 (2C), 127.9 (2C), 129.5 (2C), 130.3, 131.9, 138.1, 140.6, 143.8, 146.4, 160.6; IR (KBr): 2953, 1645, 1460, 1336, 1084, 1031 cm^{-1}; HRMS (EI) m/z: $[M^+]$ calcd for $C_{30}H_{35}NO_2S$ 473.2389; found 473.2389.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copy of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Synthetic schemes of ligands; see the Supporting Information.