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Formal Enantioselective Total Synthesis of Schulzeines A−C via Pd−Catalyzed Intramolecular Asymmetric Allylic Amination

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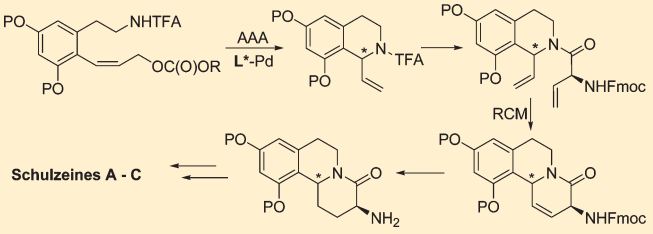
Supporting Information

ABSTRACT: Formal enantioselective total synthesis of schulzeines A−C was accomplished, featuring highly efficient Pd-catalyzed asymmetric allylic amination using novel diphosphonite ligands (BOPs) to provide 1-vinyltetrahydroisoquinoline key intermediates, as well as Ru-catalyzed ring-closing metathesis reaction to construct the key tricyclic cores in enantiopure form with correct absolute configurations.



INTRODUCTION

Schulzeines A−C, isolated from the marine sponge, *Penares schulzei*, have been identified as a new class of marine natural products (Figure 1).[1] These new alkaloids were found to exhibit potent α-glucosidase inhibitory activity, which made them promising leads in drug development for the treatment of cancer, diabetes, and viral infections.[2−4] Therefore, it is important to develop efficient syntheses for these natural products to provide sufficient amounts for biological studies as well as structure−activity relationship studies for discovery of more potent analogues.

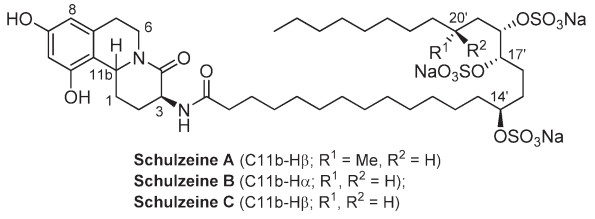
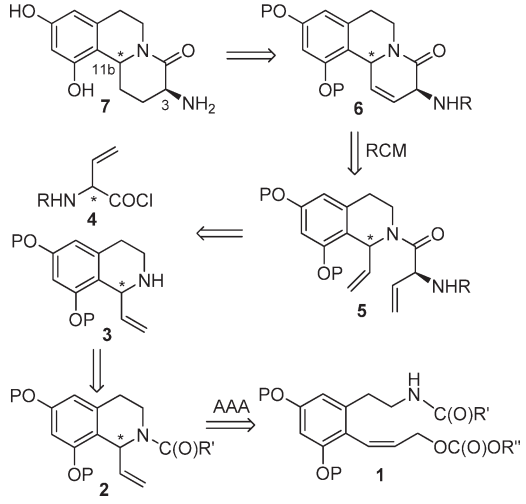


Figure 1. Schulzeines A−C.

Five research groups have reported the synthesis of schulzeines A−C tricyclic core to date.[5−9] All but one of these syntheses employed Pictet−Spengler-type cyclization to form the central ring of the tricyclic core, and the introduction of the critical stereocenter at C-11b was either totally nonselective or gave only low to moderate diastereoselectivity, wherein the separation of two diastereomers was difficult in some cases. Thus, it is apparent that a more efficient construction of the tricyclic core needs to be developed. We envisioned that an intramolecular asymmetric allylic amination (AAA) could serve as the key reaction in the construction of required stereochemistry at C11b. We describe here a new and efficient synthesis of the tricyclic core of schulzeines A−C based on the AAA approach.

Our retrosynthetic analysis is illustrated in Scheme 1. The *S* configuration to the C3 position of the tricyclic core **7** can be introduced by coupling (*S*)-vinylglycine derivative **4** to the amine

Scheme 1. Retrosynthetic Analysis of the Tricyclic Core of Schulzeines A−C



moiety of 1-vinyltetrahydroisoquinoline **3** (for representative approaches to the construction of 1-vinyltetrahydroisoquinolines, see refs 10−15), followed by ring-closing metathesis (RCM) of **5**[16] and hydrogenation of the resulting didehydropiperidinone ring of **6**. Then, **3** can be derived from **2** by N-deprotection, and **2** with excellent enantiopurity can be obtained through the intramolecular AAA of **1**, which should introduce the chiral center at C11b of **7**.

RESULTS AND DISCUSSION

The AAA substrate **1A** (P = 4-methoxybenzyl (PMB), R′ = CF_3) was prepared from the *N*-trifluoroacetyl-*O*,*O*′-bis-PMB-resorcinolamine (**8A**) as shown in Scheme 2. The iodination of **8A** (TFA = trifluoroacetyl) with *N*-iodosuccinimide (NIS)[17] proceeded

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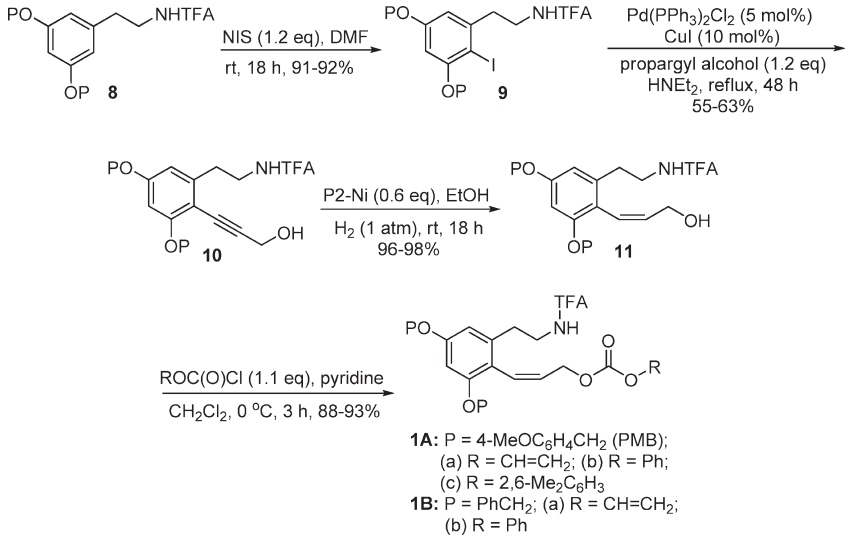
Scheme 2. Preparation of AAA Substrate 1A-a−c



smoothly to give **9A**. No bis-iodinated product was detected by TLC. The Sonogashira coupling of **9A** with propargyl alcohol gave **10A** in fairly good yield (60−65%), wherein conversion was 80−85% after 48 h (15−20% **9A** was recovered). Selective hydrogenation of **10A** over P2−Ni catalyst under ambient conditions gave cis-allylic alcohol **11A** cleanly. The subsequent acylation of the alcohol moiety with chloroformates gave the corresponding allylic carbonates, i.e., AAA substrates **1A-a−c** in excellent yields. In the same manner, AAA substrates **1B-a,b** were prepared from *N*-trifluoroacetyl-*O*,*O*′-dibenzylresorcinolamine (**8B**) in similar yields. [Note: Compound **8** (**A** or **B**) can be prepared in two steps from commercially available resorcinolamine. Alternatively, **8** (**A** or **B**) can also be prepared from commercially available 3,5-dihydroxybenzaldehyde through PMB or benzyl protection and nitroaldol reaction, followed by reduction and trifluoroacetylation. See Experimental Section.]

Because our chiral monodentate phosphoramidite ligands gave excellent results for the intramolecular AAA reaction of a closely related catechol-based substrate,[18] several phosphoramidite ligands were examined for the reaction of **1** (P = Me, R′ = CF_3, R″ = CH═CH_2). However, to our surprise, those chiral ligands gave **2** (P = Me, R′ = CF_3) with only low to moderate enantioselectivity (Scheme 1).[19] As we reported previously,[18] chiral P−N ligands exhibited low catalytic activity, requiring 12−23 days to achieve good yield and high enantioselectivity in the presence of a strong base.[13] Also, a typical "DPPBA ligand", (1*R*,2*R*)-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl)-1,2-diaminocyclohexane,[20] did not achieve appreciable yield even after 2 days at room temperature. Therefore, we examined the novel chiral biphenol-based diphosphonite ligands (BOP ligands), which we had successfully developed for an *inter*molecular AAA reaction.[21] In addition to the previously reported BOP ligands (**L1a**−**d**), a library of new 3,3′-dibenzylbiphenol-based BOP ligands (**L1e**−**L2c**) were designed and synthesized (Figure 2) and their efficacy was examined in the AAA reaction of **1**. For the synthesis of BOP ligands, see the Experimental Section and ref 21.

First, BOP ligands **L1a**−**d** were screened for the AAA reaction of **1A-a** to give **2A** using $Pd_2(dba)_3$ (dba = dibenzylideneacetone) as the catalyst precursor in DMF at room temperature under

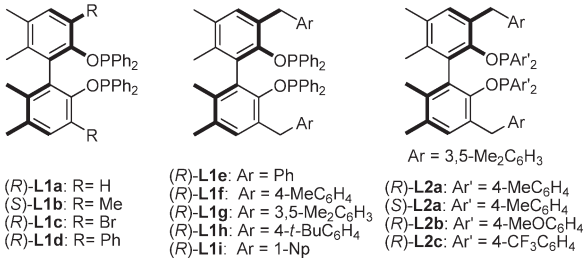


Figure 2. BOP ligand library (only *R* configuration is depicted for simplicity).

nitrogen (Scheme 3). As shown in Table 1, all reactions gave >95% conversion in less than 6 h. There was a dramatic increase in enantioselectivity when the 3,3′-substituents were changed from hydrogen (entry 1) to methyl and other groups (entries 2−4). Among the four BOP ligands examined, (*S*)-**L1b** (R = Me), gave (−)-**2A** with 80% ee (entry 2). Accordingly, we also carried out the reaction of **1B-a** and **1B-b** to see if there was a difference in enantioselectivity, depending on the protecting group of the phenolic hydroxyl groups (Scheme 3). The reactions of **1B-a** and **1B-b** under the same conditions as those for **1A-a** were completed in 2 and 6 h, respectively, to afford (−)-**2B** (P = $PhCH_2$) in high yield (>95% conversion) with 75% ee and 76% ee, respectively. Thus, **1A-a** appeared to be a better substrate than **1B-a** and **1B-b**. Also, it was found that there was a difficulty in separating (−)-**2B** from a small amount of dba by flash chromatography on silica gel, because of their very small difference in polarity. In contrast, there was no problem in the separation of (−)-**2A** from dba. Therefore, **1A** series substrates (P = PMB) were selected for optimization.

New BOP ligands bearing benzyl or substituted benzyl group at the 3,3′-positions were examined, as well. Results are shown in Table 2. Among the new BOP ligands screened, **L1g** (R = 3,5-dimethylbenzyl) gave the best result so far (entry 3). Thus, this BOP ligand was selected as the ligand of choice for further optimization.

Next, the effects of the concentration of the reaction mixture as well as the chiral ligand/Pd ratio on enantioselectivity were

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Scheme 3. Pd-Catalyzed AAA Reaction of 1

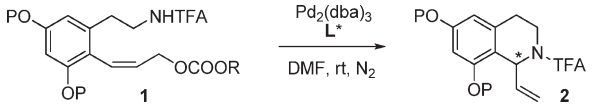
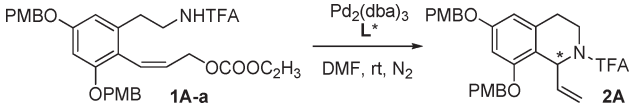


Table 1. Screening of BOP Ligands L1a−d for the AAA Reaction of 1A-a[a]



entry	ligand (**L***)	time (h)	conv (%)[b]	**2A** % ee[c]
1	(*R*)-**L1a**	1.5	>95	4 (+)
2	(*S*)-**L1b**	2	>95	80 (−)
3	(*R*)-**L1c**	5	>95	79 (+)
4	(*R*)-**L1d**	5	>95	74 (+)

[a] All reactions were run using $Pd_2(dba)_3$ (2.5 mol %) with a BOP ligand (7.5 mol %) in DMF at room temperature under N_2. [b] Determined by ^1H NMR. [c] Determined by HPLC using Chralpak AD-RH, CH_3CN/H_2O = 50/50.

Table 2. Screening of New BOP Ligands the AAA Reaction of 1A-a[a]

entry	ligand (**L***)	time (h)	conv. (%)[a]	**2A** % ee[a]
1	(*R*)-**L1e**	4	>95	83 (+)
2	(*R*)-**L1f**	4	>95	83 (+)
3	(*R*)-**L1g**	6	>95	84 (+)
4	(*R*)-**L1h**	4	>95	80 (+)
5	(*R*)-**L1i**	4	>95	80 (+)

[a] See the footnote of Table 1.

examined using (*R*)-**L1g**. As shown in Table 3, higher concentrations gave better results (entries 3 and 4) than the lower concentration (entry 1) that was employed in the screening described above. At concentrations higher than 0.5 M, Pd species precipitated out, resulting in low reactivity. Thus, we chose 0.5 M concentration for further optimization, although 0.25 M concentration afforded a slightly higher enantioselectivity, by taking into account the economical and environmental merit of using less solvent.

For the optimal ligand/Pd ratio, just the use of 1 equiv of **L1g** to Pd metal gave a bit better enantioselectivity than that achieved by using 1.5 equiv of the ligand to the metal (entry 5). Thus, the stoichiometric use of the ligand was employed for further optimization.

At this point, we examined the possible electronic effect of the diphenylphophinyl moiety of **L1g** on enantioselectivity as a further optimization process. Thus, (*R*)-**L2a-c** ligands were prepared (see Experimental Section) and their efficacy evaluated in the AAA of **1A-a** under the optimized conditions described above. As shown in Table 4, the introduction of electron-releasing substituents, i.e., Me (**L2a**) and MeO (**L2b**) groups, at the para-position of the diphenylphosphinyl moiety of **L1g** improved the efficacy (entries 2−4), while that of the electron-withdrawing CF_3 group (**L2c**) considerably descreased

Table 3. Effect of Concentration and L*/Pd Ratio on the AAA Reaction of 1A-a[a]

entry	concn (M)	L*/Pd	time (h)	conv (%)[b]	**2A** % ee[b]
1	0.05	1.5	6.0	>95	84.0 (+)
2	0.10	1.5	5.5	>95	87.5 (+)
3	0.25	1.5	5.0	>95	90.3 (+)
4	0.50	1.5	5.0	>95	90.1 (+)
5	0.50	1.0	4.5	>95	91.1 (+)

[a] Reactions were run using $Pd_2(dba)_3$ (2.5 mol %) with (*R*)-**L1g** ligand (**L***) in DMF at room temperature under N_2. [b] See the footnote of Table 1.

Table 4. Electronic Effect on the Efficacy of New BOP Ligands[a]

entry	ligand (**L***)	time (h)	conv (%)[b]	**2A** % ee[b]
1	(*R*)-**L1g**	4.5	>95	91.1 (+)
2	(*R*)-**L2a**	7	>95	94.0 (+)
3	(*S*)-**L2a**	7	>95	96.1 (−)
4	(*R*)-**L2b**	7	>95	93.3 (+)
5	(*R*)-**L2c**	7	>95	81.5 (+)

[a] Reactions were run using $Pd_2(dba)_3$ (2.5 mol %) with a BOP ligand (5.0 mol %) in DMF at room temperature. [b] See the footnote of Table 1.

Table 5. Effects of the Substrate Structure and Reaction Temperature on the AAA Reaction[a]

entry	substrate (**1A**)	temp (°C)	time (h)	conv (%)[b]	**2A** % ee[b]
1	**1A-a**	25	7	>95	94.0 (+)
2	**1A-b**	25	7	>95	93.6 (+)
3	**1A-c**	25	7	>95	92.0 (+)
4	**1A-a**	10	48	>95	95.0 (+)
5	**1A-a**	0	96	76	95.6 (+)

[a] Reactions were run using $Pd_2(dba)_3$ (2.5 mol %) with (*R*)-**L2a** ligand (5.0 mol %) in DMF at room temperature. [b] See the footnote of Table 1.

enantioselectivity (entry 5). Accordingly, (*R*)-**L2a**, which gave 94.0% ee (entry 2), was selected as the best BOP ligand for this reaction.

We also examined the effect of the allylic carbonate substituents on this AAA reaction. As shown in Table 5, the vinyl carbonate (**1A-a**) gave a slightly better result (94.0% ee) (entry 1) than the other two carbonates (**1A-b** and **1A-c**; entries 2 and 3). Effect of the reaction temperature on enantioselectivity and reaction rate was also examined. The reaction at 10 °C and 0 °C gave higher enantioselectivity (95.0 and 95.6% ee, respectively), but at 0 °C, the reaction rate was substantially decreased as compared to that at 10 °C or 25 °C (entries 4 and 5).

With the optimized conditions for the AAA reaction of **1A-a**, we prepared (+)-(*S*)-**2A** with excellent enantiopurity (94−95% ee) in a larger quantity and set out to complete the synthesis of the schulzeine B tricyclic core in accordance with the planned synthetic route (Scheme 4) based on the retrosynthetic analysis (Scheme 1) described above. [Note: The absolute configuration of (+)-**2** was tentatively assigned to *S* based on the sign of the specific rotation of close related (+)-(*S*)-1-vinyltetrahydroisoquinoline that we reported previously[18] and confirmed by the known value of (*S,S*)-**13**. See Experimental Section.] (+)-(*S*)-**2**

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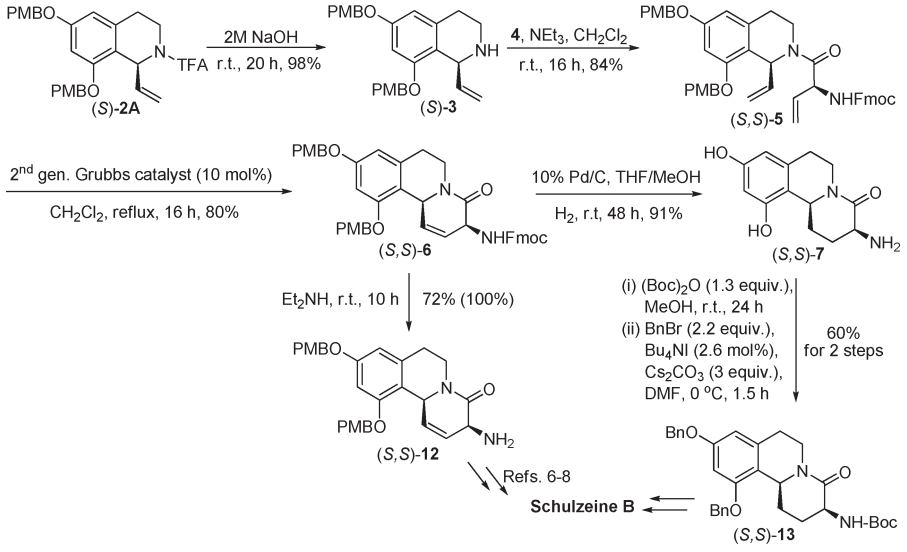
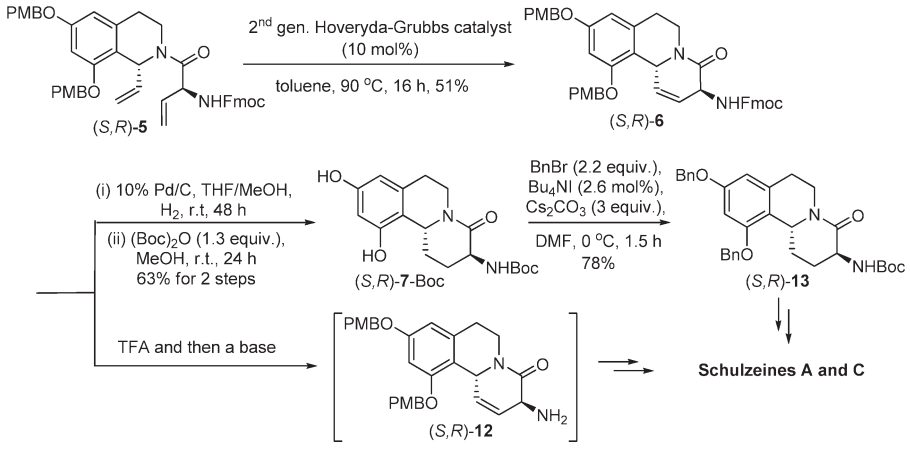
Scheme 4. Formal Total Synthesis of Schulzeine B



Scheme 5. Formal Total Synthesis of Schulzeines A and C



(94.0% ee), thus prepared, was deprotected by 2 M NaOH to give free amine **3** in 98% yield, which was reacted with *N*-Fmoc-(*S*)-vinylglycinyl chloride (**4**)[22,23] in the presence of triethylamine (1 equiv) to give (*S*,*S*)-**5** (P = PMB, R = Fmoc) with 97:3 dr. Diene **5** was subjected to RCM using the second-generation Grubbs catalyst[24] in refluxing dichloromethane to give tricyclic RCM product (*S*,*S*)-**6** as the single diastereomer in 80% yield. The hydrogenation and hydrogenolysis of (*S*,*S*)-**6** over 10% Pd/C (20 mol %) under ambient conditions for 48 h afforded the desired (*S*,*S*)-**7** in 91% yield, which was then converted to the common advanced key intermediate (*S*,*S*)-**13** through Boc and benzyl protections of the amine and resorcinol moieties. [Note: The absolute configuration at C11b of the tricylic core was assigned based on the specific rotation of (*S*,*S*)-**13**, $[\alpha]_D^{19}$ −109.2 (*c* 0.76, $CHCl_3$), with that of the literature value from the Bowen and Wardrop paper,[8] $[\alpha]_D^{24}$ −108.1 (*c* 1.96, $CHCl_3$). We also prepared (*S*,*S*)-**7**·HBr salt with $[\alpha]_D^{20}$ −138.9 (*c* 0.72, MeOH). This value was found to be virtually identical to that of the literature value for (*S*,*S*)-**7** (free amine form) from the Liu and Romo paper,[7] $[\alpha]_D^{23}$ −138.7 (*c* 0.73, MeOH). Because the free amine, (*S*,*S*)-**7**, in our hands showed the specific rotation of $[\alpha]_D^{20}$ −252.3 (*c* 0.35, MeOH), it appears that the reported value of (*S*,*S*)-**7** is an error.[7]] From (*S*,*S*)-**13**, three groups already reported the total synthesis of schulzeine B.[6−8] Thus, a formal total synthesis of this compound has been completed. Although *O*,*O*′-dibenzyl protection was used in the known total syntheses, *O*,*O*′-bis-PMB protection should work equally well. Thus, (*S*,*S*)-**12** was also prepared as an alternative key advanced intermediate through Fmoc deprotection of (*S*,*S*)-**6** with diethylamine in DCM at room temperature for 10 h.

In the same manner, we carried out the asymmetric synthesis of (*S*,*R*)-**6**, (*S*,*R*)-**7**-Boc, and **13**, starting from (−)-(*R*)-**2A**, which was obtained in 96.1% ee through the AAA reaction of **1A-a** using (*S*)-**L2a** (Scheme 5). Diene (*S*,*R*)-**5** was prepared and subjected to the RCM reaction in the same manner as that for (*S*,*S*)-**5** to give the corresponding RCM product (*S*,*R*)-**6**. However, unexpectedly, substantial epimerization occurred during the RCM reaction to give almost an equal amount of (*R*,*R*)-**6**.

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[Note: The PM3 energy calculation performed with the Spartan 2008 program indicates that *cis*-**6** and *trans*-**6** have almost same energy, and an attempted epimerization of *trans*-**6** to *cis*-**6** under the RCM conditions did not cause any epimerization. Thus, this epimerization should have taken place during the RCM reaction.] After screening of RCM catalysts and reaction variables, we found that the second-generation Hoveyda−Grubbs catalyst[25] gave the best result, so far, favoring the formation of (*S*,*R*)-**6** in 3:1 ratio. Thus, enantio- and diastereopure (*S*,*R*)-**6** was isolated in 51% yield. From (*S*,*R*)-**6**, (*S*,*R*)-7-Boc and (*S*,*R*)-**13** were synthesized in a similar manner to that illustrated in Scheme 4, and thus the formal total synthesis of schulzeines A and C have also been completed.

CONCLUSIONS

A new approach toward the total synthesis of schulzeines A−C, featuring efficient asymmetric allylic amination and ring-closing metathesis as key steps has been successfully developed. Every step in the synthesis gave good to excellent yield except for the formation of (*S*,*R*)-**6.** Further optimizations of the whole process, especially the RCM step for (*S*,*R*)-**5** and mechanistic studies are actively underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. ^{1}H, ^{13}C, and ^{31}P NMR were measured on a 500 MHz (500 MHz for ^{1}H, and 125 MHz for ^{13}C), a 400 MHz (400 MHz for ^{1}H; 100 MHz for ^{13}C; 162 MHz for ^{31}P), or a 300 MHz (300 MHz for ^{1}H; 75 MHz for ^{13}C; 121.5 MHz for ^{31}P) NMR spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm, C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in reverse phase was carried out using a Chiralpak AD-RH analytical column. Melting points were measured on a capillary melting point apparatus and are uncorrected. Optical rotations were measured on a polarimeter. TLC analyses were performed using aluminum pre-coated silica gel plates. Flash column chromatography was carried out using silica gel (particle size 40−63 μm). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana−Champaign, Urbana, IL. Unless otherwise noted all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Materials. Solvents were reagents grade and freshly distilled before use and diethyl ether (Et_2O) were dried and degassed using a solvent purification system. Toluene and methanol (MeOH) were distilled from calcium hydride. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased and used without further purification. Other solvents were used without purification. Benzylidene[1,3-bis(2,4,6trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (2nd-generation Grubbs catalyst), [1,3-bis(2,4,6-trimethylphenyl)2-imidazolidinylidene]dichloro(*o*-isopropoxyphenylmethylene)ruthenium (2nd-generation Hoveyda−Grubbs catalyst), and *N*-iodosuccinimide were purchased and used as received. (*S*)-*N*-Fmoc-vinylglycinyl chloride was synthesized in five steps from commercial available L-methionine methyl ester hydrochloride.[22] 3,5-Dibenzyloxybenzaldehyde was prepared from commercially available 3,5-dihydroxybenzaldehyde by the reported procedure.[26] Other chemicals and reagents were purchased and used without further purification unless otherwise noted. Chiral biphenols and chiral BOP ligands, **L1a**−**L1i** were prepared according to the procedure previously reported by our laboratory.[21]

3,5-Bis(4-methoxybenzyloxy)benzaldehyde. To a stirred solution of 3,5-dihydroxybenzaldehyde (4.50 g, 32.6 mmol) and K_2CO_3 (6 equiv) in DMF (150 mL) was added 4-methoxybenzyl chloride (9.60 mL, 71.7 mmol) at room temperature. Then, the mixture was stirred at 70 °C for 4 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (75 mL) and water (75 mL). The organic layer was separated and washed with water (100 mL × 3). The organic layer was then washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford crude yellow solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded 3,5-bis(4-methoxybenzyloxy)benzaldehyde as a white solid (9.48 g, 77% yield): mp 70−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 6H), 5.01 (s, 4H), 6.84 (t, J = 2.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 4H), 7.09 (d, J = 2.1 Hz, 2H), 7.35 (d, J = 8.4 Hz, 4H), 9.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 70.4, 106.1, 108.5, 108.9, 114.3, 128.5, 129.5, 138.6, 159.9, 160.6, 192.0; HRMS (ESI+) calcd For $C_{23}H_{22}O_5Na$ $[M + Na]^+$ 401.1365, found 401.1366 (Δ = 0.2 ppm).

1,3-Bis(4-methoxybenzyloxy)-5-[(E)-2-nitroethenyl]benzene. A mixture of 3,5-bis(4-methoxybenzyloxy)benzaldehyde (7.62 g, 20.2 mmol), $CH_3CO_2NH_4$ (1.56 g, 20.2 mmol), and CH_3NO_2 (106 mL) was placed in a 250 mL round-bottomed flask. Then, the mixture was heated to reflux (about 110 °C) for 1.5 h. The reaction mixture was cooled to room temperature and diluted with Et_2O (100 mL) and water (100 mL). The aqueous layer was separated and extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford crude yellow solid, which was washed with EtOH to afford 1,3-bis(4-methoxybenzyloxy)-5-[(*E*)-2-nitroethenyl] benzene as a yellow solid (7.21 g, 85% yield): mp 128−130 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 6H), 4.99 (s, 4H), 6.73 (m, 3H), 6.93 (d, J = 8.7 Hz, 4H), 7.34 (d, J = 8.7 Hz, 4H), 7.51 (d, J = 13.5 Hz, 1H), 7.90 (d, J = 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 70.4, 106.1, 108.4, 114.3, 128.4, 129.5, 131.9, 137.7, 139.3, 159.9, 160.6; HRMS (ESI+) calcd For $C_{24}H_{23}NO_6Na$ $[M + Na]^+$ 444.1423, found 444.1422 (Δ = −0.2 ppm).

*1,3-Bis(4-methoxybenzyloxy)-5-[2-(N-trifluoroacetamido)ethyl]benzene (**8A**).* To a suspension of $LiAlH_4$ (2.54 g, 66.4 mmol) in THF (50 mL) was added dropwise a solution of 1,3-bis(4-methoxybenzyloxy)-5-[(*E*)-2-nitroethenyl]benzene (6.98 g, 16.6 mmol) in THF (120 mL) at 0 °C under nitrogen. Then, the mixture was heated to 65 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with Et_2O (30 mL), and quenched with 20% KOH (50 mL) at 0 °C. The resulting precipitate was removed by filtration, and the aqueous layer was separated and extracted with Et_2O (50 mL × 3). The combined organic layer was washed with brine and dried over anhydrous K_2CO_3. The drying agent was removed by filtration, and the solvent was concentrated in vacuo to afford the crude product as brown oil. The brown oil was dissolved in DCM (120 mL), and NEt_3 (5.77 mL, 41.5 mmol) was added. To this mixture was added slowly $(CF_3CO)_2O$ (3.04 mL, 21.6 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and water (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with DCM (50 mL × 3). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as a brown solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 20:1→5:1) afforded **8A** as a white solid (4.68 g, 58% yield for two steps): mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (t, J = 6.6 Hz, 2H), 3.60 (q, J = 6.6 Hz, 2H), 3.82 (s, 6H), 4.94 (s, 4H), 6.26 (br, 1H), 6.41 (d, J = 2.4 Hz, 2H), 6.51 (t, J = 2.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 4H), 7.34 (d, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3, 40.9, 55.5, 70.1, 100.8, 107.9, 114.3, 116.0 (q, J = 286 Hz), 128.9, 129.5, 139.9, 157.3 (q, J = 37 Hz), 159.7, 160.6; HRMS (ESI+) calcd For $C_{26}H_{27}NO_5F_3$ $[M + H]^+$ 490.1841, found 490.1840 (Δ = −0.2 ppm).

*2,4-Bis(4-methoxybenzyloxy)-1-iodo-6-[2-(trifluoroacetamido)ethyl)]benzene (**9A**).* To a solution of **8A** (3.26 g, 6.65 mmol) in anhydrous DMF (12 mL) was added *N*-iodosuccinimide (NIS) (1.87 g, 8.31 mmol) all at once at room temperature. The mixture was stirred at room temperature until TLC indicated the completion of the reaction (18 h). The reaction mixture was then diluted with EtOAc (50 mL) and filtered through a pad of Celite. The filtrate was washed with distilled water (50 mL), and the aqueous layer was extracted with EtOAc (50 mL × 2). The combined organic layer was washed with saturated Na_2SO_3 (50 mL × 2) and brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as a yellow solid. Recrystallization of the crude product from hexanes/EtOAc (4/1) afforded **9A** as a white solid (3.71 g, 91% yield): mp 134−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (t, J = 6.9 Hz, 2H), 3.64 (q, J = 6.9 Hz, 2H), 3.82 (s, 6H), 4.93 (s, 2H), 5.03 (s, 2H), 6.34 (br, 1H), 6.45 (d, J = 2.7 Hz, 1H), 6.51 (d, J = 2.7 Hz, 1H), 6.92 (d, J = 8.7 Hz, 4H), 7.32 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9, 40.0, 55.4, 55.5, 70.3, 71.2, 82.9, 100.2, 108.6, 114.2, 114.3, 116.0 (q, J = 287 Hz), 128.5, 128.6, 128.9, 129.5, 142.6, 157.5 (q, J = 37 Hz), 158.6, 159.6, 159.9, 160.5; HRMS (ESI+) calcd for $C_{26}H_{25}NO_5F_3NaI$ $[M + Na]^+$ 638.0627, found 638.0626 (Δ = −0.2 ppm).

*1,3-Bis(4-methoxybenzyloxy)-6-(3-hydroxyprop-1-ynyl)-5-[2-(trifluoroacetamido)ethyl]benzene (**10A**).* A mixture of **9A** (1.52 g, 2.47 mmol), $Pd(PPh_3)_2Cl_2$ (86.7 mg, 0.124 mmol), and CuI (47.0 mg, 0.247 mmol) was placed in a 50 mL round-bottomed flask. After purging the flask with nitrogen, Et_2NH (30 mL) was added to the mixture, and the solution was stirred for 20 min at 30 °C to dissolve **9A**. Propargyl alcohol (0.29 mL, 4.94 mmol) was added to this mixture via a syringe at the same temperature. The reaction mixture was heated to reflux until TLC indicated the completion of the reaction (48 h). Then, saturated NH_4Cl solution (25 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as brown oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 5:1→1:1) afforded **10A** as an off-white solid (851 mg, 63% yield): mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (t, J = 6.3 Hz, 1H), 3.03 (t, J = 7.2 Hz, 2H), 3.64 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.53 (d, J = 6.3 Hz, 2H), 4.93 (s, 2H), 4.93 (s, 2H), 5.05 (s, 2H), 6.42 (d, J = 2.1 Hz, 1H), 6.45 (d, J = 2.1 Hz, 1H), 6.63 (br, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 40.7, 52.0, 55.5, 55.6, 70.2, 70.7, 80.2, 95.2, 99.8, 105.6, 107.9, 114.2, 114.3, 116.0 (q, J = 286 Hz), 128.5, 128.8, 128.9, 129.5, 142.9, 157.6 (q, J = 37 Hz), 159.6, 159.9, 160.1, 161.1; HRMS (ESI+) calcd For $C_{29}H_{29}NO_6F_3$ $[M + H]^+$ 544.1947, found 544.1947 (Δ = 0.0 ppm).

*1,3-Bis(4-methoxybenzyloxy)-6-[(Z)-3-hydroxyprop-1-enyl]5-[2-(trifluoroacetamido)ethyl]benzene (**11A**).* P2−Ni catalyst was generated in situ by adding $NaBH_4$ (85.9 mg, 1.70 mmol) to a suspension of $Ni(OAc)_2$ (271.3 mg, 0.893 mmol) in EtOH (7 mL) at room temperature under nitrogen with stirring. After 30 min, neat ethylenediamine (140 μL, 2.05 mmol) was added to the reaction mixture via a syringe. After the catalyst solution was stirred for another 10 min, **10A** (790 mg, 1.45 mmol) in EtOH (50 mL) was added. The nitrogen atmosphere was then replaced by hydrogen (1 atm). The reaction mixture was stirred until TLC indicated the completion of the reaction (18 h). The reaction was quenched by addition of water (20 mL), and the aqueous layer was extracted with EtOAc (25 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as an off-white solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 7:3→1:1) afforded **11A** as a white solid (759 mg, 96% yield): mp 74−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (m, 1H), 2.83 (t, J = 6.9 Hz, 2H), 3.54 (q, J = 6.9 Hz, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 3.92 (dd, J = 0.9, 7.2 Hz, 2H), 4.91 (s, 2H), 4.95 (s, 2H), 6.01 (dt, J = 7.2, 10.8 Hz, 1H), 6.31 (d, J = 10.8 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.47 (br, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2, 40.0, 55.5, 55.6, 60.5, 70.2, 70.9, 100.0, 107.8, 114.3, 114.4, 116.0 (q, J = 287 Hz), 118.4, 124.8, 128.6, 128.9, 129.4, 129.5, 133.5, 138.3, 157.2, 157.4 (q, J = 38 Hz), 159.4, 159.8; HRMS (ESI+) calcd For $C_{29}H_{30}NO_6F_3Na$ $[M + Na]^+$ 568.1923, found 568.1918 (Δ = −0.9 ppm).

*1,3-Bis(4-methoxybenzyloxy)-6-(3-ethenyloxycarbonyloxyprop-1-enyl)-[2-(trifluoroacetamido)ethyl]benzene (**1A-a**).* To a solution of **11A** (221 mg, 0.404 mmol) and pyridine (0.8 mL) in DCM (8 mL) was added slowly vinyl chloroformate (0.050 mL, 0.48 mmol) in DCM (2.4 mL) at 0 °C. After the mixture was stirred at 0 °C for 3 h, the reaction was quenched by saturated $CuSO_4$ (10 mL). The aqueous layer was separated and extracted with Et_2O (15 mL × 4). Combined organic layer was washed with water and brine and dried over anhydroud $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as an off-white solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 5:1→7:3) afforded **1A-a** as a white solid (231 mg, 93% yield): mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (t, J = 6.6 Hz, 2H), 3.54 (q, J = 6.6 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.51 (dd, J = 1.2, 6.3 Hz, 2H), 4.55 (dd, J = 2.1, 6.3 Hz, 1H), 4.88 (dd, J = 2.1, 13.8 Hz, 1H), 4.91 (s, 2H), 4.94 (s, 2H), 5.90 (dt, J = 6.3, 11.1 Hz, 1H), 6.42 (d, J = 2.1 Hz, 1H), 6.46 (dt, J = 2.1, 11.1 Hz, 1H), 6.55 (d, J = 2.1 Hz, 1H), 6.68 (br, 1H), 6.89 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.88−6.95 (m, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 39.5, 55.5, 55.6, 66.9, 70.2, 70.6, 98.3, 99.8, 107.9, 114.2, 114.3, 116.0 (q, J = 287 Hz), 117.0, 127.0, 127.4, 128.8, 128.9, 129.3, 129.6, 138.5, 142.6, 153.1, 157.4, 157.5 (q, J = 38 Hz), 159.7, 159.8; HRMS (ESI+) calcd For $C_{32}H_{32}NO_8F_3Na$ $[M + Na]^+$ 638.1978, found 638.1979 (Δ = 0.2 ppm).

*1,3-Bis(4-methoxybenzyloxy)-6-(3-phenoxycarbonyloxyprop-1-enyl)-[2-(trifluoroacetamido)ethyl]benzene (**1A-b**).* The carbonate **1A-b** was synthesized in the same manner as that described for **1A-a**: White solid (88% yield); mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.88 (t, J = 6.6 Hz, 2H), 3.51 (q, J = 6.6 Hz, 2H), 4.60 (d, J = 6.6 Hz, 2H), 4.90 (s, 2H), 4.92 (s, 2H), 5.92 (dt, J = 6.6, 11.1 Hz, 1H), 6.39 (d, J = 2.1 Hz, 1H), 6.48 (d, J = 11.1 Hz, 1H), 6.55 (d, J = 2.1 Hz, 1H), 6.66 (br, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.04−7.37 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 39.4, 55.5, 55.6, 67.0, 70.1, 70.6, 99.8, 107.9, 114.2, 114.3, 115.9 (q, J = 286 Hz), 117.1, 121.1, 126.3, 127.1, 127.4, 128.8, 128.9, 129.3, 129.5, 129.6, 138.5, 151.2, 154.1, 157.3, 157.4 (q, J = 37 Hz), 159.6, 159.7, 159.8; HRMS (ESI+) calcd For $C_{36}H_{34}NO_8F_3Na$ $[M + Na]^+$ 688.2134, found 688.2131 (Δ = −0.4 ppm).

*1,3-Bis(4-methoxybenzyloxy)-6-[3-(2,6-dimethylphen-1-oxy)carbonyloxyprop-1-enyl]-[2-(trifluoroacetamido)ethyl]benzene (**1A-c**).* The carbonate **1A-c** was synthesized in the same manner as that described for **1A-a**: Colorless oil (92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 6H), 2.88 (t, J = 6.8 Hz, 2H), 3.49 (q, J = 6.8 Hz, 2H), 3.82 (s, 6H), 4.57 (dd, J = 1.2 and 6.8 Hz, 2H), 4.90 (s, 2H), 4.92 (s, 2H), 5.91 (dt, J = 6.8, 10.8 Hz, 1H), 6.39 (d, J = 2.0 Hz, 1H), 6.48 (d, J = 10.8 Hz, 1H), 6.55 (d, J = 2.0 Hz, 1H), 6.67 (t, J = 6.8 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.02 (s, 3H), 7.29 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 15.9, 32.7, 39.1, 55.3, 66.8, 69.9, 70.3, 99.6, 107.7, 113.9, 114.0, 115.7 (q, J = 282 Hz), 116.8, 126.1, 126.9, 127.2, 128.5, 128.6, 129.1, 129.3, 129.9, 138.3, 148.2, 153.3, 157.0, 157.3 (q, J = 36 Hz), 159.4, 159.5, 159.6;

HRMS (ESI+) calcd For $C_{38}H_{38}NO_8F_3Na$ $[M + Na]^+$ 716.2447, found 716.2451 (Δ = 0.6 ppm).

In the same manner as that described for **8A**−**1Aa**−**c**, **8B**−**1Ba**,**b** were prepared. Characterization data are shown below:

1,3-Dibenzyloxy-5-[(E)-2-nitroethenyl]benzene. Yellow solid; 65% yield; mp 110−112 °C; ^{1}H NMR (300 MHz, $CDC1_3$) δ 5.06 (s, 4H), 6.75 (br, 3H), 7.35−7.42 (m, 10H), 7.50 (d, J = 13.5 Hz, 1H), 7.90 (d, J = 13.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDC1_3$) δ 70.5, 106.0, 108.4, 127.7, 128.4, 128.9, 132.0, 136.4, 137.7, 139.2, 160.6; HRMS (ESI+) calcd For $C_{22}H_{20}NO_4$ $[M + H]^+$ 362.1392, found 362.1396 (Δ = 1.1 ppm).

*1,3-Dibenzyloxy-5-[2-(N-trifluoroacetamido)ethyl]benzene (**8B**).* White crystals; 55% yield for two steps from 1,3-dibenzyloxy-5-[(*E*)-nitroethenyl]benzene: mp 85−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (t, J = 6.8 Hz, 2H), 3.61 (q, J = 6.8 Hz, 2H), 5.03 (s, 4H), 6.26 (br, 1H), 6.43 (d, J = 2.4 Hz, 2H), 6.54 (t, J = 2.4 Hz, 1H), 7.32−7.43 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4, 40.9, 70.3, 100.8, 108.1, 116.0 (q, J = 286 Hz), 127.7, 128.3, 128.8, 136.9, 140.1, 157.3 (q, J = 36 Hz), 160.6; HRMS (ESI+) calcd For $C_{24}H_{23}NO_3F_3$ $[M + H]^+$ 430.1630, found 430.1629 (Δ = −0.2 ppm).

*2,4-Dibenzyloxy-1-iodo-6-[2-(trifluoroacetamido)ethyl)]benzene (**9B**).* White solid; 92% yield; mp 139−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08 (t, J = 6.9 Hz, 2H), 3.61 (q, J = 6.9 Hz, 2H), 5.00 (s, 2H), 5.10 (s, 2H), 6.37 (br, 1H), 6.46 (d, J = 2.4 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 7.31−7.50 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9, 40.0, 70.6, 71.3, 82.9, 100.1, 108.6, 116.0 (q, J = 286 Hz), 127.3, 127.7, 128.2, 128.5, 128.8, 128.9, 136.4, 136.5, 142.7, 157.5 (q, J = 36 Hz), 158.5, 160.5. HRMS (ESI+) calcd For $C_{24}H_{21}NO_3F_3NaI$ $[M + Na]^+$ 578.0416, found 578.0415 (Δ = −0.2 ppm).

*1,3-Dibenzyloxy-6-(3-hydroxyprop-1-ynyl)-5-[2-(trifluoroacetamido)ethyl]benzene (**10B**).* Off-white solid; 55% yield; mp 121−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (t, J = 6.0 Hz, 1H), 3.03 (t, J = 7.2 Hz, 2H), 3.64 (q, J = 7.2 Hz, 2H), 5.00 (s, 2H), 5.12 (s, 2H), 6.43 (d, J = 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 6.68 (br, 1H), 7.31−7.45 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 40.7, 51.9, 70.4, 70.8, 80.1, 95.3, 99.8, 105.7, 107.9, 116.0 (q, J = 287 Hz), 127.1, 127.8, 128.1, 128.4, 128.8, 128.9, 136.5, 136.8, 142.9, 157.7 (q, J = 37 Hz), 160.0, 161.0. HRMS (ESI+) calcd For $C_{27}H_{24}NO_4F_3Na$ $[M + Na]^+$ 506.1555, found 506.1551 (Δ = −0.8 ppm).

*1,3-Dibenzyloxy-6-[(Z)-3-hydroxyprop-1-enyl]-5-[2-(trifluoroacetamido)ethyl]benzene (**11B**).* White solid; 98% yield; mp 138−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (t, J = 6.9 Hz, 2H), 3.55 (q, J = 6.9 Hz, 2H), 3.94 (d, J = 7.2 Hz, 2H), 5.00 (s, 2H), 5.02 (s, 2H), 6.03 (dt, J = 7.2, 11.1 Hz, 1H), 6.34 (d, J = 11.1 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.50 (br, 1H), 6.56 (d, J = 2.4 Hz, 1H), 7.32−7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 39.9, 60.4, 70.4, 71.0, 99.9, 107.8, 116.0 (q, J = 286 Hz), 118.4, 124.8, 127.6, 127.8, 128.3, 128.4, 128.8, 128.9, 133.5, 136.7, 136.8, 138.3, 157.2, 157.5 (q, J = 36 Hz), 159.3; HRMS (ESI+) calcd For $C_{27}H_{26}NO_4F_3Na$ $[M + Na]^+$ 508.1712, found 508.1714 (Δ = 0.4 ppm).

*1,3-Dibenzyloxy-6-(3-ethenyloxycarbonyloxyprop-1-enyl)-[2-(trifluoroacetamido)ethyl]benzene (**1B-a**).* White sticky solid; 89% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (t, J = 6.9 Hz, 2H), 3.55 (q, J = 6.9 Hz, 2H), 4.55 (m, 3H), 4.88 (dd, J = 2.1, 13.8 Hz, 2H), 4.98 (s, 2H), 5.01 (s, 2H), 5.90 (dt, J = 7.2, 11.1 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 6.48 (d, J = 11.1 Hz, 1H), 6.56 (d, J = 2.1 Hz, 1H), 6.73 (br, 1H), 6.95 (dd, J = 7.2, 13.8 Hz, 1H), 7.32−7.44 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.7, 39.3, 66.6, 70.2, 70.6, 98.1, 99.6, 107.8, 115.8 (q, J = 286 Hz), 117.0, 126.9, 127.3, 127.6, 128.0, 128.1, 128.6, 136.5, 136.6, 138.4, 142.4, 152.9, 157.1, 157.5 (q, J = 37 Hz), 159.4; HRMS (ESI+) calcd For $C_{30}H_{28}NO_6F_3Na$ $[M + Na]^+$ 578.1766, found 578.1762 (Δ = −0.7 ppm).

*1,3-Dibenzyloxy-6-(3-phenoxycarbonyloxyprop-1-enyl)-[2-(trifluoroacetamido)ethyl]benzene (**1B-b**).* White solid; 91% yield; mp 112−114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (t, J = 6.6 Hz, 2H), 3.52 (q, J = 6.6 Hz, 2H), 4.60 (d, J = 6.6 Hz, 2H), 4.99 (s, 4H), 5.95 (dt, J = 6.3, 11.1 Hz, 1H), 6.40 (d, J = 2.1 Hz, 1H), 6.50 (d, J = 11.1 Hz, 1H), 6.56 (d, J = 2.1 Hz, 1H), 6.67 (br, 1H), 7.04−7.25 (m, 5H), 7.32−7.44 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 39.4, 67.0, 70.4, 70.8, 99.8, 108.0, 116.3 (q, J = 287 Hz), 117.2, 121.1, 126.3, 127.1, 127.4, 127.5, 127.8, 128.2, 128.3, 128.8, 128.9, 129.6, 136.8, 138.6, 151.1, 154.1, 157.2, 157.5 (q, J = 37 Hz), 159.6; HRMS (ESI+) calcd For $C_{34}H_{30}NO_6F_3Na$ $[M + Na]^+$ 628.1923, found 628.1917 (Δ = −1.0 ppm).

General Procedure for Intramolecular Asymmetric Allylic Amination. Typical procedure is described for the reaction of **1A-a** to afford (+)-(*S*)-6,8-bis-(4-methoxybenzyloxy)-1-ethenyl-2-trifluoroacetyl-3,4-dihydro-1*H*-isoquinoline, (+)-(*S*)-**2A**: A solution of BOP ligand (*R*)-**L2a** (28.5 mg, 0.0319 mmol) and $Pd_2(dba)_3$ (14.8 mg, 0.0159 mmol) in DMF (1.3 mL) was added to a reaction tube with a stirring bar under nitrogen. The solution was stirred at room temperature until the color of the solution turned to light yellow from purple. Then, **1A-a** (400 mg, 0.638 mmol) was added to the catalyst solution via a syringe. The mixture was stirred at room temperature until TLC indicated completion of the reaction. The resulting solution was diluted with water (20 mL). The aqueous layer was separated and extracted with Et_2O (25 mL × 3). The combined organic layer was washed with water (20 mL × 5) and brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as orange oil. The conversion of the reaction was checked by ^{1}H NMR, which indicated over 95% conversion and 100% product selectivity. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→5:1) afforded (+)-(*S*)-**2A** as a colorless oil (285 mg, 85% yield). The pure product was then subjected to chiral HPLC analysis, using a Chiralcel AD-RH column (CH_3CN/H_2O = 50/50, 0.7 mL/min), which indicated that the enantiopurity of the product (+)-(*S*)-**2A** was 94.0% ee. The *S* configuration was tentatively assigned by comparison of the sign of the optical rotation of (+)-(*S*)-**2** with that of structurally close (+)-(*S*)-1-ethenyl-2-trifluoroacetyl-6,7-dimethoxy-1,2,3,-4-tetrahydroisoquinoline and further confirmed by converting (+)-(*S*)-**2A** to literature known (−)-(*S*,*S*)-**12**[8] (see below).

(+)-(*S*)-**2A:** $[\alpha]_D^{21}$ +66.0 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) (a mixture of two rotamers) δ 2.76−2.82 (m, 1H), 2.88−3.05 (m, 1H), [3.30−3.40 (m, 0.67H), 3.58−3.66 (m, 0.33H)], 3.81 (s, 3H), 3.82 (s, 3H), [3.92−4.00 (m, 0.33H), 4.35−4.42 (m, 0.33H)], 4.93−4.99 (m, 5H), 5.19−5.24 (m, 1H), 5.87−6.00 (m, 1H), [5.80−5.84 (m, 0.67H), 6.20−6.24 (m, 0.67H)], [6.35 (d, J = 2.1 Hz, 0.67H), 6.38 (d, J = 2.1 Hz, 0.33H)], 6.48 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 7.5 Hz, 2H), 6.92 (d, J = 7.5 Hz, 2H), 7.31 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of two rotamers) (major) δ 29.5, 39.9, 51.6, 55.5, 70.0 70.1, 99.1, 105.6, 114.2, 114.3, 115.4, 116.7, 116.8 (q, J = 287 Hz), 128.8, 128.9, 129.0, 129.4, 135.1, 135.4, 155.9 (q, J = 36 Hz), 156.0, 159.1, 159.6, 159.8; (minor) δ 28.0, 38.0, 53.4, 55.5, 70.0, 70.1, 99.0, 105.9, 114.2, 114.3, 115.4, 116.8 (q, J = 287 Hz), 117.1, 128.8, 128.9, 129.0, 129.5, 135.8, 136.2, 155.8 (q, J = 36 Hz), 156.6, 159.4, 159.6, 159.8; HRMS (ESI+) calcd For $C_{29}H_{28}NO_5F_3Na$ $[M + Na]^+$ 550.1817, found 550.1818 (Δ = 0.2 ppm).

*(−)-(R)-6,8-Bis(4-methoxybenzyloxy)-1-ethenyl-2-trifluoroacetyl-3,4-dihydro-1H-isoquinoline,(−)-(R)-**2A**.* The compound (−)-(*R*)-**2A** was obtained in the same manner as that described for the synthesis of (+)-(*S*)-**2A** except for using (*S*)-**L2a** as the chiral ligand: 85% yield; 96.1% ee. All characterization data were identical to those of (+)-(*S*)-**2A** except for $[\alpha]_D^{21}$ −67.1 (*c* 1.5, CH_2Cl_2). HRMS (ESI+) calcd For $C_{29}H_{29}NO_5F_3$ $[M + H]^+$ 528.1998, found 528.1996 (Δ = −0.4 ppm).

*(−)-(R)-6,8-Dibenzyloxy-1-ethenyl-2-trifluoroacetyl-3,4-dihydro-1H-isoquinoline [(−)-(R)-**2B**].* Colorless oil; 83% yield; 75% ee; ^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of two rotamers) δ 2.73−2.85 (m, 1H), 2.90−3.06 (m, 1H), [3.32−3.42 (m, 0.36H), 3.58−3.69 (m, 0.64H)], [3.90−4.00 (m, 0.64H), 4.35−4.44 (m, 0.36H)], 4.93−5.10 (m, 5H), 5.19−5.27 (m, 1H), 5.99 (ddd, J = 4.4, 10.4, 17.2 Hz, 1H),

[5.85−5.90 (m, 0.36H), 6.25−6.30 (m, 0.64H)], [6.37 (d, J = 2.0 Hz, 0.64H), 6.39 (d, J = 2.0 Hz, 0.36H)], 6.48 (d, J = 2.0 Hz, 1H), 7.35−7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of two rotamers) (major) δ 29.5, 39.8, 51.6, 70.3 70.5, 99.1, 105.8, 115.6, 116.8 (q, J = 287 Hz), 116.9, 117.0, 117.2, 127.3, 128.3, 128.8, 135.1, 135.9, 136.8, 137.0, 155.8 (q, J = 36 Hz), 156.6, 159.1; (minor) δ 28.0, 38.0, 53.4, 70.2, 70.4, 99.0, 106.1, 115.5, 116.7, 116.8 (q, J = 287 Hz), 117.1, 117.3, 127.1, 127.7, 128.1, 135.0, 135.8, 136.3, 136.9, 155.9, 156.2 (q, J = 36 Hz), 159.1; HRMS (ESI+) calcd For $C_{27}H_{25}NO_3F_3$ $[M + H]^+$ 468.1787, found 468.1786 (Δ = −0.2 ppm).

*(+)-(S)-6,8-Bis(4-methoxybenzyloxy)-3,4-dihydro-1-ethenyl-1H-isoquinoline, (+)-(S)-**3***. To a stirred solution of (+)-(*S*)-**2A** (280 mg, 0.531 mmol, 94.0% ee) in EtOH (5 mL) was added slowly 2 M NaOH solution (1 mL) at room temperature, and the mixture was stirred at room temperature for 16 h. Then, EtOH was evaporated under reduced pressure, and the resulting oil was diluted with Et_2O (20 mL) and water (20 mL). The aqueous layer was separated and extracted with Et_2O (20 mL × 3). The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford (+)-(*S*)-**3** (225 mg, 98% yield) as a light yellow solid: mp 83−85 °C; $[\alpha]_D^{21}$ +25.8 (*c* 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61−2.66 (m, 1H), 2.78−2.90 (m, 1H), 2.97−3.04 (m, 1H), 3.09−3.20 (m, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.70 (d, J = 5.2 Hz, 1H), 4.86−4.95 (m, 5H), 5.11 (dt, J = 10.0, 1.2 Hz, 1H), 6.01−6.12 (m, 1H), 6.35 (d, J = 2.0 Hz, 1H), 6.42 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.4, 38.1, 52.6, 55.5, 69.8, 70.0, 98.5, 106.1, 114.1, 114.2, 116.2, 118.1, 128.9, 129.2, 129.3, 129.5, 136.9, 139.0, 156.8, 158.5, 159.5, 159.7; HRMS (ESI+) calcd For $C_{27}H_{30}NO_4$ $[M + H]^+$ 432.2175, found 432.2163 (Δ = −2.8 ppm).

*(−)-(R)-6,8-Bis(4-methoxybenzyloxy)-3,4-dihydro-1-ethenyl-1H-isoquinoline, (−)-(R)-**3***. The compound (−)-(*R*)-**3** was obtained in 98% yield in the same manner as that described for the synthesis of (+)-(*S*)-**3**. All characterization data were identical to those of (+)-(*S*)-**3** except for $[\alpha]_D^{21}$ −27.0 (*c* 0.62, $CHCl_3$). HRMS (ESI+) calcd For $C_{27}H_{30}NO_4$ $[M + H]^+$ 432.2175, found 432.2172 (Δ = −0.7 ppm).

*(−)-(3S,11bS)-9,11-Bis(4-methoxybenzyloxy)-3-(9H-fluoren-9-yl) methoxycarbonylamino-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (−)-(S,S)- **6***. To a stirred solution of (+)-(*S*)-**3** (94% ee) (58.3 mg, 0.135 mmol) and Et_3N (18.8 μL, 0.135 mmol) in distilled DCM (0.8 mL) was added (*S*)-*N*-Fmoc-vinylglycinyl chloride (**4**) (50.8 mg, 0.149 mmol) in DCM (2 mL) at 0 °C under nitrogen. The mixture was then stirred at room temperature for 16 h, and the reaction was quenched by adding Et_2O (10 mL) and water (10 mL). The aqueous layer was separated and extracted with Et_2O (15 mL × 2). The combined organic layer was washed with 1 M hydrochloric acid, water, and brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 5:1→2:1) afforded (+)-(*S*,*S*)-**5** as a colorless oil (83 mg, 84% yield): cis/trans > 20/1 by ^{1}H NMR); $[\alpha]_D^{21}$ +61.0 (*c* 1.0, CH_2Cl_2); HRMS (ESI+) calcd For $C_{46}H_{45}N_2O_7$ $[M + H]^+$ 737.3227, found 737.3232 (Δ = 0.7 ppm).

To a stirred solution of (+)-(*S*,*S*)-**5** (63 mg, 0.086 mmol) in DCM (3.5 mL) was added the second-generation Grubbs catalyst (7.4 mg, 10 mol %) under nitrogen, and the mixture was heated to reflux for 16 h. The reaction mixture was cooled to room temperature, and DCM was evaporated under reduced pressure to give the crude product as a brown solid. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 4:1→1:1) afforded (−)-(*S*,*S*)-**6** as a white solid (48 mg, 80% yield): mp 125−127 °C (decomp); $[\alpha]_D^{21}$ −132 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63−2.85 (m, 3H), 3.83 (s, 6H), 4.26 (t, J = 7.2 Hz, 1H), 4.41 (d, J = 7.2 Hz, 2H), 4.65−4.70 (m, 1H), 4.89−5.08 (m, 5H), 5.39 (d, J = 5.7 Hz, 1H), 5.95−6.08 (m, 2H), 6.39 (d, J = 2.4 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.90−6.95 (m, 4H), 7.26−7.40 (m, 8H), 7.62 (d, J = 6.6 Hz, 2H), 7.76 (d, J = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 40.4, 47.4, 51.5, 52.8, 55.5, 55.6, 67.4, 70.1, 70.2, 99.3, 106.1, 114.3, 114.4, 114.5, 115.8, 120.2, 125.4, 127.3, 127.9, 128.4, 128.5, 128.9, 129.0, 129.1, 129.5, 129.9, 137.9, 141.5, 144.1, 144.2, 156.4, 158.9, 159.7, 159.8, 167.5; HRMS (ESI+) calcd For $C_{44}H_{41}N_2O_7$ $[M + H]^+$ 709.2914, found 709.2906 (Δ = −1.1 ppm).

*(−)-(3S,11bS)-3-Amino-9,11-bis(4-methoxybenzyloxy)-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (−)-(S,S)-**12***. To a stirred solution of (−)-(*S*,*S*)-**6** (25 mg, 0.036 mmol) in DCM (4.0 mL) was added Et_2NH (37 μL, 0.36 mmol) at room temperature, and the mixture was stirred at room temperature for 10 h. Solvents were evaporated under reduced pressure to give the crude product as brown oil. ^{1}H NMR analysis of the crude product indicated a quantitative formation of the desired product, (−)-(*S*,*S*)-**12**. Purification of the crude product by flash column chromatography on silica gel (CH_2Cl_2/(2 M NH_3 in MeOH) = 99:1→98:2) afforded (−)-(*S*,*S*)-**12** as a light yellow oil (13 mg, 72% yield): $[\alpha]_D^{21}$ −197.8 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 2.60−2.80 (m, 3H), 3.78 (s, 6H), 3.84−3.87 (m, 1H), 4.77−4.80 (m, 1H), 4.91−5.04 (m, 4H), 5.35−5.37 (m, 1H), 5.81 (ddd, J = 2.0, 3.2, 9.6 Hz, 1H), 6.18 (ddd, J = 2.0, 3.2, 9.6 Hz, 1H), 6.41 (d, J = 2.0 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 4H), 7.31 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 29.6, 40.0, 53.8, 54.5, 69.7, 69.9, 99.1, 106.5, 113.7, 113.8, 115.9, 127.6, 128.9, 129.1, 129.3, 137.6, 156.4, 158.9, 159.8, 159.9, 171.3; HRMS (ESI+) calcd For $C_{29}H_{31}N_2O_5$ $[M + H]^+$ 487.2233, found 487.2220 (Δ = −2.7 ppm).

*(−)-(3S,11bS)-3-Amino-9,11-dihydroxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (−)-(S,S)-**7***. To (−)-(*S*,*S*)-**6** (40 mg, 0.055 mmol) and 10% Pd/C (12 mg, 0.011 mmol) placed in a 10 mL round-bottomed flask were added MeOH (1.5 mL) and THF (1.5 mL) at room temperature. The nitrogen atmosphere was then replaced with hydrogen (1 atm), and the reaction mixture was stirred for 48 h. The reaction mixture was filtered through Celite and washed with MeOH (30 mL), and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel [CH_2Cl_2/(2 M NH_3 in MeOH) = 30:1→10:1) afforded (−)-(*S*,*S*)-**7** as a white paste (13 mg, 91% yield): $[\alpha]_D^{20}$ −252.3 (*c* 0.35, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.28−1.52 (m, 3H), 2.22−2.31 (m, 1H), 2.47−2.74 (m, 4H), 3.58 (t, J = 8.1 Hz, 1H), 4.62−4.66 (m, 1H), 4.79 (dd, J = 3.6 and 14.4 Hz, 2H), 6.11 (d, J = 2.4 Hz, 1H), 6.18 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 28.1, 29.1, 30.6, 40.5, 50.8, 52.1, 102.1, 107.5, 115.5, 138.6, 156.4, 158.1, 175.2; HRMS (ESI+) calcd For $C_{13}H_{17}N_2O_3$ $[M + H]^+$ 249.1239, found 249.1232 (Δ = −2.8 ppm).

*(−)-(3S,11bS)-3-Amino-9,11-dihydroxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one Hydrobromide, (−)-(S,S)-**7**·HBr.* To (−)-(*S*,*S*)-**7** (5.5 mg, 0.022 mmol) in a 5 mL round-bottomed flask were added 16% hydrobromic acid (0.6 mL) and MeOH (2.4 mL) at room temperature, and the mixture was stirred for 4 h. All volatiles were removed under high vacuum to give (−)-(*S*,*S*)-**7**·HBr as a light yellow paste (7.3 mg, 100% yield): $[\alpha]_D^{20}$ −138.9 (*c* 0.73, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 1.41−1.56 (m, 1H), 1.67−1.83 (m, 1H), 2.35−2.53 (m, 2H), 2.66−2.86 (m, 3H), 4.21 (dt, J = 7.8, 11.7 Hz, 1H), 4.44−4.51 (m, 1H), 4.82−4.84 (m, 1H), 6.25−6.41 (m, 2H); ^{13}C NMR (125 MHz, D_2O): δ 22.3, 27.0, 28.4, 39.5, 48.8, 49.8, 101.3, 107.1, 114.4, 138.3, 153.9, 155.4, 168.3; LRMS (ESI-) calcd For $C_{13}H_{17}N_2O_3Br$ $[M - H]^-$ 327.0, found 327; HRMS (ESI+) calcd For $C_{13}H_{17}N_2O_3$ $[M - Br]^+$ 249.1239, found 249.1237 (Δ = −0.8 ppm).

*(−)-(3S,11bS)-3-(tert-Butoxycarbonylamino)-9,11-dihydroxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (−)-(S,S)-**7**-Boc.*[6] To a stirred solution of (−)-(*S*,*S*)-**7** (5.8 mg, 0.023 mmol) in

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MeOH (0.5 mL) was added Boc_2O (7.4 mg, 0.030 mmol) under nitrogen, and the mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure to give the crude product as a light yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 4:1→1:1) afforded (−)-(*S*,*S*)-7-Boc as colorless oil (6.4 mg, 79% yield): $[\alpha]_D^{22}$ −176.6 (*c* 0.64, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.28−1.40 (m, 1H), 1.42 (s, 9H), 1.46−1.55 (m, 1H), 2.22−2.37 (m, 1H), 2.48−2.52 (m, 1H), 2.59−2.75 (m, 3H), 4.32 (t, *J* = 8.4 Hz, 1H), 4.59−4.62 (m, 1H), 4.80−4.81 (m, 1H), 6.11 (d, *J* = 2.4 Hz, 1H), 6.18 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 26.3, 28.7, 29.2, 30.3, 40.4, 50.8, 51.2, 80.5, 102.0, 107.3, 115.1, 138.4, 156.3, 158.0, 158.2, 172.4. All data are in agreement with the literature values except for the specific rotation. Gurjar et al.[6] reported the specific rotation of this compound to be $[\alpha]_D$ −49.1 (*c* 0.90, MeOH). However, the value was $[\alpha]_D^{22}$ −176.6 (*c* 0.64, MeOH) in our hands, as shown above. It appears that the reported value is either an error or their compound is enantiomerically not pure.

*(−)-(3S,11bS)-3-(tert-Butoxycarbonylamino)-9,11-bis(benzyloxy)-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (−)-(S,S)-**13***. To a stirred solution of (*S*,*S*)-7-Boc (6.4 mg, 0.019 mmol), tetrabutylammonium iodide (TBAI) (0.2 mg, 0.0005 mmol), and Cs_2CO_3 (18 mg, 0.057 mmol) in DMF (0.5 mL) was added benzyl bromide (0.026 mL, 0.042 mmol) at 0 °C under nitrogen, and the mixture was stirred under the same temperature for 3 h. The reaction was quenched with water (5 mL) and diluted with EtOAc (5 mL). The aqueous layer was separated and extracted with EtOAc (5 mL × 2). The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as a light yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 10:1→4:1) afforded (−)-(*S*,*S*)-**13** as a colorless oil (7.6 mg, 78% yield): $[\alpha]_D^{19}$ −109.2 (*c* 0.76, $CHCl_3$) [lit.[8] $[\alpha]_D^{24}$ −108.1 (*c* 1.97, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35−1.42 (m, 2H), 1.46 (s, 9H), 2.41−2.60 (m, 2H), 2.71−2.82 (m, 3H), 4.30−4.36 (m, 1H), 4.72−4.76 (m, 1H), 4.89−4.92 (m, 1H), 5.00 (s, 2H), 5.07 (s, 2H), 5.75 (d, *J* = 5.2 Hz, 1H), 6.39 (d, *J* = 2.1 Hz, 1H), 6.48 (d, *J* = 2.1 Hz, 1H), 7.30−7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 28.6, 28.7, 29.9, 39.0, 49.0, 50.0, 70.4, 79.7, 99.2, 106.0, 117.6, 127.4, 127.7, 128.3, 128.4, 128.8, 129.0, 136.7, 136.9, 137.5, 155.9, 156.2, 158.7, 170.8. All data are in good agreement with those reported by Bowen and Wardrop.[8] However, the specific rotation reported by Gurjar et al.[6] was $[\alpha]_D$ −102 (*c* 1.1, $CHCl_3$), which is considerably lower than our value as well as that of Bowen and Wardrop.

*(+)-(3S,11R)-9,11-Bis(4-methoxybenzyloxy)-3-(9H-fluoren-9-yl)methoxycarbonylamino-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (+)-(S,R)-**6***. To a stirred solution of (−)-(*R*)-**3** (96.1% ee) (76.5 mg, 0.177 mmol) and Et_3N (24.6 μL, 0.177 mmol) in DCM (1 mL) was added **4** (72.7 mg, 0.212 mmol) in DCM (3 mL) at 0 °C under nitrogen, and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with Et_2O (10 mL) and water (10 mL). The aqueous layer was separated and extracted with Et_2O (15 mL × 2). The combined organic layer was washed with 1 M hydrochloric acid, water, and brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent evaporated in vacuo to afford the crude product as yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 5:1→2:1) afforded (−)-(*S*,*R*)-**5** as colorless oil (105 mg, 81% yield): trans/cis > 20/1 by ^{1}H NMR; $[\alpha]_D^{20}$ −36.8 (*c* 1.25, CH_2Cl_2); HRMS (ESI+) calcd For $C_{46}H_{45}N_2O_7$ $[M + H]^+$ 737.3227, found 737.3218 (Δ = −1.2 ppm).

To a stirred solution of (−)-(*S*,*R*)-**5** (41 mg, 0.055 mmol) in toluene (5.5 mL) was added second generation Hoveyda−Grubbs catalyst (7.0 mg, 20 mol %) under nitrogen, and the mixture was heated to 90 °C for 40 h. The reaction mixture was cooled to room temperature, and toluene was evaporated under reduced pressure to give the crude product as a brown solid. The ^{1}H NMR analysis of the crude product indicated that (*S*,*R*)-**6** and (*R*,*R*)-**6** were formed in 3:1 ratio. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 2:1→1:1) afforded (*S*,*R*)-**6** as an off-white solid (20 mg, 51% yield). Because (+)-(*S*,*R*)-**6** was found to be rather unstable and prone to decompose, the purified compound was immediately used for the next step without further characterization.

*(+)-(3S,11bR)-3-(tert-Butoxycarbonylamino)-9,11-dihydroxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (+)-(S,R)-**7**-Boc.* To (+)-(*S*,*R*)-**6** (20 mg, 0.028 mmol), thus obtained, and 10% Pd/C (6.0 mg, 0.0056 mmol) placed in a 5 mL round-bottomed flask were added MeOH (0.8 mL) and THF (0.8 mL) at room temperature. The nitrogen atmosphere was then replaced with hydrogen (1 atm). The mixture was stirred at room temperature for 48 h, and Boc_2O (9.0 mg, 0.036 mmol) in MeOH (0.2 mL) was added without removing Pd/C. The reaction mixture was stirred at room temperature for 20 h. The solid was then filtered, and the filtrate was evaporated under reduced pressure to give the crude product as a light yellow oil. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc = 2:1→1:1) afforded (+)-(*S*,*R*)-7-Boc as colorless oil (6.1 mg, 63% yield for two steps): $[\alpha]_D^{20}$ +184.3 (*c* 0.51, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.34−1.51 (m, 1H), 1.45 (s, 9H), 1.91−2.12 (m, 2H), 2.49−2.70 (m, 3H), 3.05−3.09 (m, 1H), 3.92−4.05 (m, 1H), 4.73−4.79 (m, 2H), 6.08 (d, *J* = 2.1 Hz, 1H), 6.16 (d, *J* = 2.1 Hz, 1H). ^{1}H NMR data are in agreement with the literature values. Gurjar et al.[6] reported the specific rotation of this compound to be $[\alpha]_D$ +122 (*c* 1.4, MeOH). However, the value was $[\alpha]_D^{20}$ +184.3 (*c* 0.51, MeOH) in our hands, as shown above. It appears that the reported value is either an error or their compound is enantiomerically not pure.

*(+)-(3S,11bR)-3-(tert-Butoxycarbonylamino)-9,11-bis(benzyloxy)-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one, (+)-(S,R)-**13***. Compound (+)-(*S*,*R*)-**13** was obtained in 78% yield as colorless oil in the same manner as that described for the synthesis of (−)-(*S*,*S*)-**13**: $[\alpha]_D^{19}$ +177.2 (*c* 0.57, $CHCl_3$) [lit.[8] $[\alpha]_D^{24}$ +182.2 (*c* 1.33, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40−1.53 (m, 1H), 1.45 (s, 9H), 1.69−1.75 (m, 1H), 2.41−2.49 (m, 1H), 2.57−2.66 (m, 2H), 2.83−2.90 (m, 1H), 3.04−3.08 (m, 1H), 3.99−4.06 (m, 1H), 4.78 (dd, *J* = 3.6, 11.2 Hz, 1H), 4.89−4.94 (m, 1H), 4.98−5.08 (m, 4H), 5.32 (br s, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 7.32−7.42 (m, 10H). ^{1}H NMR data are in agreement with the literature values.[8]

Gurjar et al.[6] reported the specific rotation of this compounds to be $[\alpha]_D$ +116 (*c* 1.35, MeOH). However, the value was $[\alpha]_D^{19}$ +177.2 (*c* 0.57, $CHCl_3$) in our hands and $[\alpha]_D^{24}$ +182.2 (*c* 1.33, $CHCl_3$) by Bowen and Wardrop,[8] as shown above. It appears that the reported value by Gurjar et al.[6] is either an error or their compound is enantiomerically not pure. We believe that a small difference in our specific rotation and that by Bowen and Wardrop[8] is due to the difference in concentration and temperature for the measurement.

General Procedure for the Synthesis of Chiral Diphosphonite Ligands. To a solution of a chiral biphenol[12] (1 mmol), DMAP (10 mol %) and Et_3N (0.8 mL, 6 mmol) in DCM (10 mL) at 0 °C was added a solution of a chlorodiarylphosphine (2.5 mmol) in DCM (5 mL) over the period of 20 min via a syringe. The mixture was stirred at the same temperature for additional 3 h and concentrated in vacuo. The residue was dissolved in dry Et_2O (20 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the crude product was purified on a silica gel column pretreated with Et_3N using (hexanes: NEt_3 = 99:1) as the eluent.

*(R)-2,2′-Bis[bis(4-methylphenyl)phosphinoxy]-3,3′-bis(3,5-dimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl, (R)-**L2a***. Colorless oil; 50% yield; $[\alpha]_D^{21}$ −72.5 (*c* 0.69, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.81 (s, 6H), 2.22 (s, 18H), 2.27 (s, 6H), 3.45

(d, J = 15.6 Hz, 2H), 3.57 (d, J = 15.6 Hz, 2H), 6.34 (s, 2H), 6.63 (s, 4H), 6.81 (t, J = 8.1 Hz, 6H), 7.01 (d, J = 7.8 Hz, 4H), 7.15 (t, J = 7.8 Hz, 4H), 7.31 (t, J = 7.8 Hz, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 111.0; HRMS (EI) calcd $C_{62}H_{64}O_4P_2$ $[M + O_2]^+$ 934.4280, found 934.4267 (Δ = −1.3 ppm).

*(S)-2,2′-Bis[bis(4-methylphenyl)phosphinyloxy]-3,3′-bis(3,5-dimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl, (S)-**L2a***. Colorless oil; 45% yield; $[\alpha]_D^{21}$ +74.4 (c 0.73, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.81 (s, 6H), 2.22 (s, 18H), 2.27 (s, 6H), 3.45 (d, J = 15.6 Hz, 2H), 3.57 (d, J = 15.6 Hz, 2H), 6.34 (s, 2H), 6.63 (s, 4H), 6.81 (t, J = 8.1 Hz, 6H), 7.01 (d, J = 7.8 Hz, 4H), 7.15 (t, J = 7.8 Hz, 4H), 7.31 (t, J = 7.8 Hz, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 110.9; HRMS (EI) calcd $C_{62}H_{64}O_2P_2$ $[M]^+$ 902.4382, found 902.4399 (Δ = 1.7 ppm).

*(R)-2,2′-Bis[bis(4-methoxyphenyl)phosphinyloxy]-3,3′-bis(3,5-dimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl, (R)-**L2b***. Colorless oil; 62% yield; $[\alpha]_D^{21}$ −31.4 (c 0.51, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.67 (s, 6H), 1.84 (s, 6H), 2.22 (s, 12H), 3.44 (d, J = 15.3 Hz, 2H), 3.60 (d, J = 15.3 Hz, 2H), 3.69 (s, 6H), 3.75 (s, 6H), 6.39 (s, 2H), 6.64 (s, 4H), 6.53 (d, J = 8.4 Hz, 4H), 6.66 (s, 4H), 6.76−6.79 (m, 4H), 7.16−7.21 (m, 4H), 7.33−7.38 (m, 4H); ^{31}P NMR (121.5 Hz, CD_2Cl_2) δ 112.7; HRMS (EI) calcd $C_{62}H_{64}O_8P_2$ $[M + O_2]^+$ 998.4076, found 998.4059 (Δ = −1.4 ppm).

*(R)-2,2′-Bis[bis(4-trifluoromethylphenyl)phosphinyloxy]-3,3′-bis(3,5-dimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl, (R)-**L2c***. Colorless oil; 35% yield; $[\alpha]_D^{23}$ −115.8 (c 1.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 6H), 1.86 (s, 6H), 2.19 (s, 12H), 3.40 (d, J = 15.6 Hz, 2H), 3.62 (d, J = 15.6 Hz, 2H), 6.42 (s, 2H), 6.49 (s, 4H), 6.77 (s, 2H), 7.30−7.44 (m, 14H) ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 103.5; HRMS (EI) calcd $C_{62}H_{52}O_2F_{12}P_2$ $[M]^+$ 1118.3251, found 1118.3233 (Δ = −1.8 ppm).

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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