JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

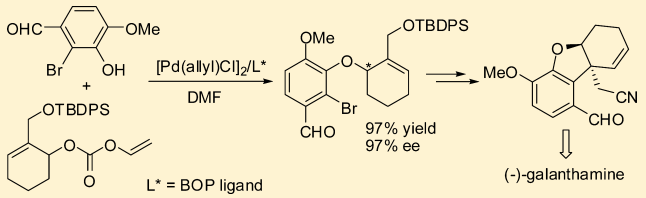
Pd-Catalyzed Asymmetric Allylic Etherification Using Chiral Biphenol-Based Diphosphinite Ligands and Its Application for The Formal Total Synthesis of (−)-Galanthamine

Yang Zang and Iwao Ojima*

Department of Chemistry, Stony Brook University, Stony Brook, New York 11794-3400, United States

Supporting Information

ABSTRACT: A library of novel chiral biphenol-based diphosphinite (BOP) ligands was designed and created. These BOP ligands were applied to a Pd-catalyzed intermolecular allylic etherification reaction, which provided a key intermediate for the formal total synthesis of (−)-galanthamine with 97% ee in 97% yield.



INTRODUCTION

Galanthamine (Figure 1), an amaryllidaceae alkaloid,[1,2] has been used for the treatment of mild to moderate Alzheimer's disease and other memory impairments.[3] Galanthamine reversibly inhibits acetylcholine esterase (Ache).[4,5] Because the isolation from natural sources is tedious, expensive, and insufficient for clinical use, many chemical syntheses have been reported.[6−14] In addition, a biomimetic synthesis through phenol coupling followed by dynamic resolution has been performed on a pilot scale.[15] However, only a few approaches to the asymmetric total synthesis of (−)-galanthamine have been reported.[16−20] One of the most efficient methods was reported by Trost et al., wherein the critical chiral centers were created by Pd-catalyzed intermolecular asymmetric allylic etherification.[16−18] The best results achieved so far in the key step using his "modular" diphosphine ligand, DPPBA, were 88% ee and 72% yield, and recrystallization was required in the subsequent step to afford the key intermediate **6** (96% ee) bearing a tricyclic benzofuran skeleton with a chiral quaternary carbon (Scheme 1).[18] In addition, **6** is a versatile intermediate for the syntheses of (−)-morphine and its derivatives, (−)-codeine and (−)-thebaine (Figure 1).[18] Accordingly, this useful process to provide **6** still needs substantial improvement in its enantioselectivity and chemical yield to be more practical.

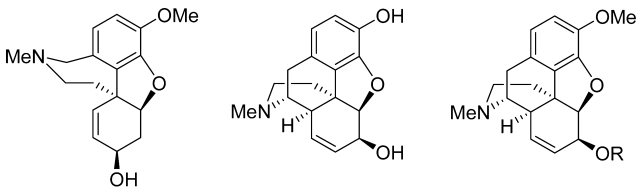


Figure 1. (−)-Galanthamine, (−)-morphine, and its derivatives.

We have been developing a library of novel chiral biphenol-based monodentate phosphites and phosphoramidites as well as bidentate diphosphinite ligands (BOP ligands) for a variety of catalytic asymmetric reactions.[21−28] As compared to common 1,1′-binaphthol-based diphosphinite (BINAPO) ligands,[29,30] the novel BOP ligands have exhibited much higher efficiency in intramolecular and intermolecular palladium-catalyzed asymmetric allylic amination (AAA) reaction (up to 96% ee).[27,28] One of the salient features of BOP ligands is their fine-tuning capability through modification of the substituents at the 3,3′-positions of the biphenyl moiety as well as the aromatic groups attached to the phosphorus atoms (Figure 2). Thus, we have examined the efficacy of the BOP ligands (reported and new) in the intermolecular asymmetric allylic etherification (AAE) reaction by following Trost's approach to (−)-galanthamine and optimizing the enantioselectivity and chemical yield for the synthesis of the key intermediate **6**.

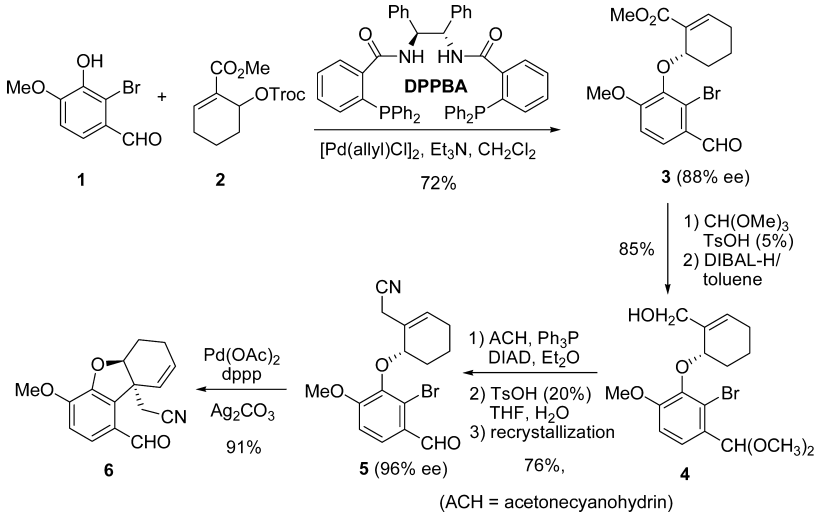
RESULTS AND DISSCUSION

We investigated the AAE reaction of phenol **1** and allylic carbonates **7** instead of **2** in Trost's synthesis. Since the ester moiety of **2** was reduced to a hyroxymethyl group later in Trost's synthesis, we decided to use a protected hydroxymethyl group in the allylic carbonate **7** from the beginning. It was reported that the methyl ester moiety at the 2-position of **2** was essential for the reaction to take place under Trost's conditions, and no reactions took place when other substrates bearing nonester moieties were at the 2-position. We have recently used **7a** and **7b** for the successful intermolecular AAA reaction.[27] Initial screening of the allylic carbonates **7a−c** was performed using the BOP ligand, (*R*)-L**1f**, under conditions nearly identical to those used for the previously reported intermolecular Pd-catalyzed AAA reaction.[27] Thus, the reactions were carried out in DMF at a substrate concentration of 0.025 M with a Pd/(*R*)-L**1f** ratio of 1:1.5. Results are summarized in Table 1.

Received: February 16, 2013
Published: March 11, 2013

dx.doi.org/10.1021/jo400355j | J. Org. Chem. 2013, 78, 4013−4018

Scheme 1. Trost's Total Synthesis of (−)-Galanthamine



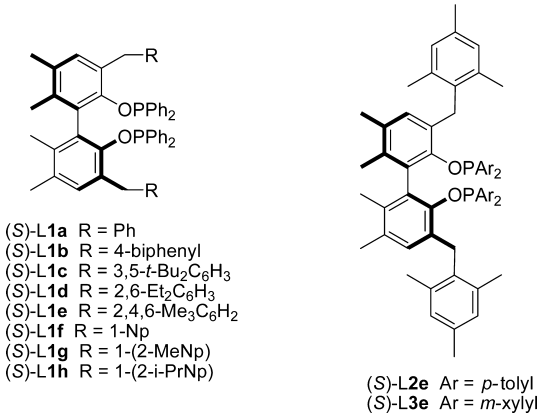
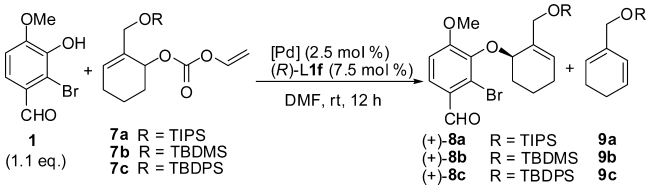


Figure 2. BOP ligand library (only *S* configuration is shown for simplicity).

Table 1. Initial Screening of Allylic Substrates 7a−c

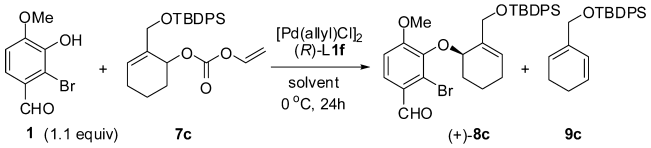


entry	substrate	catalyst	conv[a] (%)	(+)-**8** (% ee)[b]	(+)-**8**:**9**[a]
1	**7a**	$Pd_2(dba)_3$	>95	54 (+)	80:20
2	**7b**	$Pd_2(dba)_3$	>95	62 (+)	79:21
3	**7c**	$Pd_2(dba)_3$	>95	72 (+)	82:18
4	**7c**	$[Pd(allyl)Cl]_2$	>95	80 (+)	85:15

[a]Determined by ^{1}H NMR. [b]Determined by HPLC using Chiralcel OJ after desilylation with TBAF.

As Table 1 shows, the aryl ethers (+)-**8a−c** were obtained in good yields in all reactions, but together with byproduct **9a−c**.[27,31] It is of interest to note that the formation of this type of byproduct was not reported by Trost et al., who used **2** instead of **7**.[16−18] An increase in enantioselectivity for the formation of (+)-**8** was observed as the size of the silyl group increased (Table 1, entries 1−3). Switching the Pd-catalyst precursor Pd(0) ($Pd_2(dba)_3$) to Pd(II) ($[Pd(allyl)Cl]_2$) increased the enantioselectivity to 80% ee (Table 1, entry 4). All reactions were complete within 12 h at room temperature. Lowering the reaction temperature to 0 °C slightly increased the enantioselectivity to 82% ee (see Table 2, entry1), but the reaction was naturally slowed down.

Table 2. Effect of Solvents



entry	solvent	conv (%)[a,b]	(+)-**8c** (% ee)[a,b]	(+)-**8c**:**9c**[a,b]
1	DMF	>95	82 (+)	90:10
2	CH_3CN	65	86 (+)	92:8
3	CH_2Cl_2	46	86 (+)	93:7
4[c]	CH_3CN	>95	84 (+)	89:11
5[c]	CH_2Cl_2	76	84 (+)	91:9

[a,b]See the footnotes of Table 1. [c]1.1 equiv of TEA was added.

The effect of solvents on this reaction was also examined using **7c** as the allylic substrate and $[Pd(allyl)Cl]_2$ as the catalyst precursor at 0 °C for 24 h. As Table 2 shows, the reactions run in CH_3CN and CH_2Cl_2 gave (+)-**8c** with 86% ee, but with only 46−65% conversion (Table 2, entries 2 and 3). It was found that phenol **1** precipitated out in these solvents at 0 °C. Then, the addition of 1.1 equiv of triethylamine (TEA) was found to solve or improve this problem and the reactions proceeded much more smoothly, especially in CH_3CN (Table 2, entries 4 and 5).

Next, BOP ligands were screened using **7c** as the allylic substrate, CH_3CN as the solvent, and TEA (1.1 equiv) as the additive at 0 °C for 24 h. The results are summarized in Table 3. (The result when (*R*)-L**1f** from Table 2 was used is included for comparison.) It should be noted that, at this point, we screened (*S*)-BOP ligands since the key intermediate **5** for (−)-galanthamine should have the (−)-(*S*) configuration, and thus **8** should also have the (−)-(*S*) configuration, which was found to be achieved by using (*S*)-BOP ligands based on the results shown above.

As Table 3 shows, (*S*)-L**1b** bearing a 4-phenylbenzyl group at the 3,3′-positions afforded (−)-**8c** with 78% ee (Table 3, entry

dx.doi.org/10.1021/jo400355j | J. Org. Chem. 2013, 78, 4013−4018

Table 3. Screening of BOP Ligands[a]

entry	ligand	conv[b,c] (%)	**8c** (% ee)[b,c]	**8c**:**9c**[b,c]
1	(*S*)-L**1a**	>95	79 (−)	92:8
2	(*S*)-L**1b**	>95	78 (−)	92:8
3	(*S*)-L**1c**	78	69 (−)	87:13
4	(*S*)-L**1d**	90	90 (−)	90:10
5	(*S*)-L**1e**	>95	91 (−)	92:8
6	(*R*)-L**1f**	>95	84 (+)	89:11
7	(*S*)-L**1g**	89	90 (−)	89:11
8	(*S*)-L**1h**	83	90 (−)	88:12

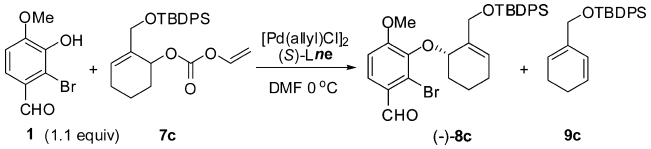
[a]Reactions were run using **7c** (0.025 M), $[Pd(allyl)Cl]_2$ (2.5 mol %) with a BOP ligand (7.5 mol %), and 1.1 equiv of TEA in CH_3CN at 0 °C for 24 h. [b,c]See the footnote of Table 1.

2), which was close to the results using 3,3′-unsubstituted ligand (*S*)-L**1a** (Table 3, entry 1). However, the introduction of a bulky substituent at the *meta* position, i.e., the 3,5-di-*tert*-butylbenzyl group at the 3,3′-positions, i.e., (*S*)-L**1c**, resulted in a substantial decrease in enantioselectivity as well as conversion (Table 3, entry 3). In contrast to the *para* and *meta* substitutions, a significant increase in enantioselectivity was observed when ligands bearing an *ortho*-substituted benzyl group, including 2,6-disubstituted and 2,4,6-trisubsituted benzyl groups, was used at the 3,3′-positions, i.e., (*S*)-L**1d**−**h** (Table 3, entries 4−8). It should be noted that the introduction of very bulky benzyl groups, such as 2-methylnaphth-1-ylmethyl [(*S*)-L**1g**], and 2-isopropylnaphth-1-ylmethyl [(*S*)-L**1h**], slightly reduced the reaction rate and product selectivity, but enantioselectivity was not affected (Table 3, entries 7 and 8). Among the BOP ligands screened, (*S*)-L**1e** gave the best result (Table 3, entry 5). Thus, (*S*)-L**1e** was selected for further optimization. At this point, we also ran the reaction with (*S*)-L**1e** in DMF and found that the same enantioselectivity (91% ee) was obtained without addition of TEA, and the product selectivity was improved to 94:6 (see Table 4, entry 1).

For further optimization of (*S*)-L**1e**, two new BOP ligands bearing *p*-tolyl [(*S*)-L**2e**] and *m*-xylyl [(*S*)-L**3e**] groups in the diarylphosphorus moieties were designed and prepared. Their efficacy was evaluated under the same conditions as those employed for ligand (*S*)-L**1e**. As Table 4 shows, the introduction of a *p*-tolyl group [(*S*)-L**2e**] slightly decreased the enantioselectivity (88% ee) and reaction rate (Table 4, entry 2), while that of a *m*-xylyl group [(*S*)-L**3e**] considerably increased the enantioselectivity to 97% ee with very good product selectivity (93:7) but slowed down the reaction (Table 4, entry 3). Accordingly, the reaction was run at a higher concentration of **7c** (0.1 M), which gave a moderate increase in conversion (Table 4, entry 4). Thus, this substrate concentration was used in the subsequent reactions as well. To our delight, 97% ee with full conversion (>95% by ^{1}H NMR analysis wherein no **7c** was observed) after 36 h was achieved by increasing the Pd catalyst precursor loading to 5 mol % (Table 4, entry5). When the reaction was run at room temperature, the reaction was complete within 12 h and (−)-**8c** was obtained with 94% ee (Table 4, entry 6). Addition of TEA at 0 °C accelerated the reaction, but enantioselectivity was 94% ee (Table 4, entry 7).

With the optimized condition for the asymmetric allylic etherification, we prepared (−)-**8c** with 97% ee and 97% isolated yield using a small excess of **7c** (1.2 equiv) to increase the product yield; i.e., phenol **1** became the limiting reactant under these conditions (Scheme 2). Deprotection of (−)-**8c** with TBAF afforded allylic alcohol **10** in 99% yield. The key intermediate, nitrile **5**, was prepared in good yield (71% for two steps) by treatment of **10** with MsCl/TEA and then NaCN in DMSO. The crucial tricylic key intermediate **6** for the total synthesis of (−)-galanthamine was obtained in 90% yield through intramolecular Heck reaction. Thus, the critical intermediate **6** was obtained via **5** steps in 61% overall yield from **1**. As compared to Trost's original work (42% yield for six steps from **1**),[18] our synthesis of **6** has made significant improvement in that substantial enhancement of enantioselectivity (97% ee vs 88% ee) was achieved in the AAE step so that recrystallization of **5** is not necessary and the protection and deprotection of aldehyde (−)-**8c** is not required.

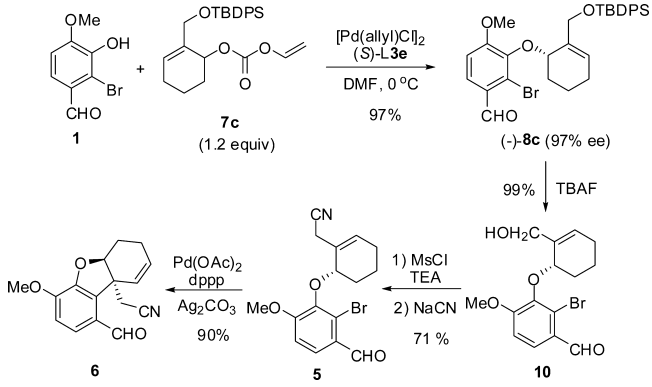
Table 4. Optimization of BOP Ligands and Conditions[a]



entry	ligand	time (h)	conv[b,c] (%)	(−)-**8c** (% ee)[b,c]	(−)-**8c**:**9c**[b,c]
1	(*S*)-L**1e**	24	>95	91 (−)	94:6
2	(*S*)-L**2e**	24	85	88 (−)	95:5
3	(*S*)-L**3e**	24	41	97 (−)	93:7
4[d]	(*S*)-L**3e**	24	51	97 (−)	89:11
5[d,e]	(*S*)-L**3e**	36	>95	97 (−)	91:9
6[d,f]	(*S*)-L**3e**	12	>95	94 (−)	83:17
7[d,g]	(*S*)-L**3e**	12	>95	94 (−)	83:17

[a]Reactions were run using **7c** (0.025 M) and $[Pd(allyl)Cl]_2$ (2.5 mol %) with a BOP ligand (7.5 mol %) in DMF at 0 °C. [b,c]See the footnote of Table 1. [d]At 0.1 M concentration of **7c**. [e]5 mol % of $[Pd(allyl)Cl]_2$ and 15 mol % of (*S*)-L**3e**. [f]At room temperature. [g]1.1 equiv of TEA was added.

Scheme 2. Synthesis of the Key Intermediate 6



CONCLUSIONS

A new series of BOP ligands have been developed that exhibit excellent efficacy when applied to the Pd-catalyzed AAE reaction, leading to the formal total synthesis of (−)-galanthamine. The results presented here further demonstrate the advantages of readily fine-tuning capability of our BOP ligands for a specific process in a variety of catalytic asymmetric reactions, including the AAE reaction. Further applications of BOP ligands as well as other biphenol-based chiral phosphorus ligands are currently underway in our laboratory.

dx.doi.org/10.1021/jo400355j | J. Org. Chem. 2013, 78, 4013−4018

EXPERIMENTAL SECTION

General Methods. ^{1}H, ^{13}C, and ^{31}P NMR were measured on a 500 MHz (500 MHz for ^{1}H; 125 MHz for ^{13}C), 400 MHz (400 MHz for ^{1}H; 100 MHz for ^{13}C; 162 MHz for ^{31}P), or 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) as the internal standard or phosphoric acid as the external reference (^{31}P 0.00 ppm). Analytical HPLC in the normal phase was carried out using a Chiralcel OJ analytical column. Melting points were measured on a capillary melting point apparatus and are uncorrected. Optical rotations were measured on a digital polarimeter. TLC analyses were performed using aluminum-precoated silica gel plates. Flash column chromatography was carried out using silica gel (particle size 40−63 μm). High-resolution mass data were obtained using electron-impact (EI+) or time-of-flight (TOF) mass spectrometry. Unless otherwise noted, all reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques.

Material. Solvents were reagent grade and freshly dried, degassed, and distilled before use. Anhydrous *N*,*N*-dimethylformamide (DMF) and acetonitrile were obtained commercially and used without further purification. Chemicals and reagents were purchased from commercial sources and used without further purification unless otherwise noted. 2-Bromo-3-hydroxy-4-methoxybenzaldehyde (**1**) was prepared following the reported procedure.[18] Chiral BOP ligands, (*S*)-**L1a** and (*R*)-**L1f**, were synthesized according to the procedure previously reported by our laboratory.[27,28] 2-Hydroxymethyl-2-cyclohexenol,[30,31] allylic vinyl carbonates **7a**[27,30] and **7b**[27] were prepared by the literature methods.

(*S*)-3,3′-Bis(2,4,6-trimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diol ((*S*)-B1e). A solution of mesitylmagnesium bromide in tetrahydrofuran (THF, 1 M, 3 mL) was added at 0 °C to a solution of (*S*)-3,3′-bis(chloromethyl)-2,2′-dimethoxy-5,5′,6,6′-tetramethyl-1,1′-biphenyl[27] (366 mg, 1 mmol) in THF (10 mL) containing CuI (48 mg, 0.125 mmol) over 30 min. The mixture was warmed to room temperature and stirred for an additional 30 min and then at 50 °C for 10 h. The reaction was quenched with aqueous NH_4Cl solution (20 mL), and the reaction mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was directly used for the next step without further purification.

Boron tribromide (2.2 mL, 1 M solution in CH_2Cl_2) was added dropwise over 20 min to a stirred solution of the previous crude product in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by the slow addition of water. The aqueous layer was extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/AcOEt = 50:1 to 30:1) to afford (*S*)-**B1e** (476 mg, 94% over two steps) as a white foam: mp 185−186 °C; $[\alpha]^{21}_D$ −20.0 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 6H), 2.12 (s, 6H), 2.25 (s, 12H), 2.33 (s, 6H), 3.95 (d, *J* = 17 Hz, 2H), 4.00 (d, *J* = 17 Hz, 2H), 4.76 (s, 2H), 6.45 (s, 2H), 6.93 (s, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.0, 19.9, 20.0, 20.9, 28.2, 119.7, 123.5, 128.8, 128.8, 129.8, 133.6, 133.9, 135.4, 137.2, 149.5; HRMS (EI+) calcd for $C_{36}H_{42}O_2$ $[M]^+$ 506.3185, found 506.3193 (Δ = 1.6 ppm).

In the same manner, chiral biphenols (*S*)-B**1b**−**d** and (*S*)-B**1g**−**h** were synthesized.

(*S*)-3,3′-Bis(4-phenylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diol ((*S*)-B1b): white foam; 534 mg; yield 93%; mp 141−142 °C; $[\alpha]^{21}_D$ +10.8 (*c* 0.65, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 6H), 2.28 (s, 6H), 4.06 (d, *J* = 15.2 Hz, 2H), 4.11 (d, *J* = 15.2 Hz, 2H), 4.72 (s, 2H), 7.06 (s, 2H), 7.38 (m, 6H), 7.46 (m, 4H), 7.57 (d, *J* = 7.8 Hz, 4H), 7.63 (d, *J* = 7.8 Hz, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.3, 19.9, 35.6, 120.5, 124.7, 127.1, 127.1, 127.2, 128.8, 129.1, 129.2, 132.6, 134.9, 138.9, 140.3, 141.2, 149.7; HRMS (EI+) calcd for $C_{42}H_{38}O_2$ $[M]^+$ 574.2872, found 574.2869 (Δ = −0.5 ppm).

(*S*)-3,3′-Bis(3,5-di-*tert*-butylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diol ((*S*)-B1c): white foam; 575 mg; yield 89%; mp 80−81 °C; $[\alpha]^{21}_D$ +40.0 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 36H), 1.88 (s, 6H), 2.21 (s, 6H), 3.92 (d, *J* = 15.2 Hz, 2H), 4.04 (d, *J* = 15.2 Hz, 2H), 4.62 (s, 2H), 6.97 (s, 2H), 7.10 (s, 4H), 7.26 (s, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.2, 19.8, 31.5, 34.8, 36.2, 119.9, 120.6, 122.9, 124.8, 128.8, 132.5, 134.4, 140.0, 149.5, 150.6; HRMS (EI+) calcd for $C_{46}H_{62}O_2$ $[M]^+$ 646.4750, found 646.4743 (Δ = −1.1 ppm).

(*S*)-3,3′-Bis(2,6-diethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diol ((*S*)-B1d): white foam; 449 mg; yield 84%; mp 170−171 °C; $[\alpha]^{21}_D$ −14.9 (*c* 0.47, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.5 Hz, 12H), 1.90 (s, 6H), 2.12 (s, 6H), 2.65 (q, *J* = 7.5 Hz, 8H), 4.05 (d, *J* = 17.2 Hz, 2H), 4.12 (d, *J* = 17.2 Hz, 2H), 4.81 (s, 2H), 6.45 (s, 2H), 7.17 (d, *J* = 7.5 Hz, 4H), 7.26 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 15.4, 16.0, 19.8, 26.4, 27.1, 119.6, 124.4, 126.2, 126.6, 128.8, 130.3, 133.9, 135.2, 143.4, 149.2; HRMS (EI+) calcd for $C_{38}H_{46}O_2$ $[M]^+$ 534.3498, found 534.3491 (Δ = −1.3 ppm).

(*S*)-3,3′-Bis(2-methylnaphthalen-1-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diol ((*S*)-B1g): white foam; 484 mg; yield 88%; mp 127−128 °C; $[\alpha]^{21}_D$ −12.2 (*c* 0.74, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 6H), 2.02 (s, 6H), 2.54 (s, 6H), 4.47 (s, 4H), 4.94 (s, 2H), 6.42 (s, 2H), 7.43 (m, 6H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 6.9 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.1, 19.8, 20.5, 27.4, 119.8, 123.8, 124.3, 124.6, 126.0, 126.7, 128.4, 129.0, 129.2, 130.5, 132.6, 133.1, 133.4, 134.2, 134.5, 149.2; HRMS (EI+) calcd for $C_{40}H_{38}O_2$ $[M]^+$ 550.2872, found 550.2863 (Δ = −1.6 ppm).

(*S*)-3,3′-Bis(2-isopropylnaphthalen-1-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl-2,2′-diol ((*S*)-B1h): white foam; 527 mg; yield 87%; mp 125−126 °C; $[\alpha]^{21}_D$ −12.9 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.7 Hz, 12H), 1.89 (s, 6H), 2.02 (s, 6H), 3.46 (m, 2H), 4.49 (d, *J* = 18.6 Hz, 2H), 4.54 (d, *J* = 18.6 Hz, 2H), 4.94 (s, 2H), 6.45 (s, 2H), 7.43 (m, 4H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.82 (m 4H), 7.99 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.1, 19.8, 23.9, 23.9, 26.6, 29.8, 119.7, 123.9, 124.5, 124.7, 124.9, 126.1, 127.3, 128.3, 128.9, 130.8, 131.4, 132.4, 133.1, 134.1, 144.8, 149.0; HRMS (EI+) calcd for $C_{44}H_{46}O_2$ $[M]^+$ 606.3498, found 606.3507 (Δ = 1.5 ppm).

(*S*)-2,2′-Bisdiphenylphosphinoxy-3,3′-bis(2,4,6-trimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*S*)-L1e). A solution of chlorodiphenylphosphine (221 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added slowly over 20 min to a solution of an enantiopure biphenol (*S*)-B**1e** (202 mg, 0.4 mmol), 4-*N*,*N*-dimethylaminopyridine (DMAP) (5 mg, 0.04 mmol), and triethylamine (TEA) (0.3 mL, 2.5 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred at the same temperature for an additional 2 h. The reaction mixture was then concentrated in vacuo. The residue was dissolved in ether (4 mL) and filtered through a pad of Celite. The filtrate was concentrated again, and the crude product was purified on a silica gel column pretreated with TEA by using hexanes/AcOEt (50:1) as the eluent to afford (*S*)-L**1e** (248 mg, 71%) as a white foam: mp 95−97 °C; $[\alpha]^{21}_D$ +127.6 (*c* 0.29, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 6H), 1.83 (s, 6H), 2.03 (s, 12H), 2.28 (s, 6H), 3.49 (d, *J* = 16.8 Hz, 2H), 3.66 (d, *J* = 16.8 Hz, 2H), 6.06 (s, 2H), 6.82 (s, 4H), 7.18 (m, 12H), 7.38 (m, 8H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.7, 20.0, 20.9, 29.9, 127.7, 127.9, 128.2, 128.5, 129.0, 129.2, 130.2, 130.3, 131.4, 134.1, 134.2, 135.1, 137.2, 151.9; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 108.75; HRMS (ESI+) calcd for $C_{60}H_{61}O_2P_2$ $[M + H]^+$ 875.4147, found 875.4165 (Δ = 1.8 ppm).

In the same manner, BOP ligands, (*S*)-**L1b**-**d**, (*S*)-**L1g**-**h**, and (*S*)-**L2**−**3e** were synthesized.

(*S*)-2,2′-Bisdiphenylphosphinoxy-3,3′-bis(4-phenylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*S*)-L1b:). white foam; 264 mg; yield 70%; mp 85−87 °C; $[\alpha]^{21}_D$ +130.0 (*c* 0.29, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 6H), 1.90 (s, 6H), 3.55 (d, *J* = 15.9 Hz, 2H), 3.72 (d, *J* = 15.9 Hz, 2H), 6.48 (s, 2H), 7.02 (d, *J* = 8.0 Hz, 4H), 7.16 (m, 12H), 7.39 (m, 18H), 7. 58 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 17.0, 19.9, 36.0, 126.7, 126.9, 127.7, 127.8,

dx.doi.org/10.1021/jo400355j | J. Org. Chem. 2013, 78, 4013−4018

128.7, 128.7, 128.8, 128.9, 129.5, 129.8, 130.6, 131.1, 131.6, 134.9, 138.3, 140.3, 141.2, 151.8; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 110.63; HRMS (ESI+) calcd for $C_{66}H_{57}O_2P_2$ $[M + H]^+$ 943.3834, found 943.3858 (Δ = 2.5 ppm).

(*S*)-2,2′-Bisdiphenylphosphinoxy-3,3′-bis(3,5-di-*tert*-butylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*S*)-L1c): white foam; 329 mg; yield 81%; mp 81−83 °C; $[\alpha]^{21}_D$ +77.1 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 36H), 1.75 (s, 6H), 1.82 (s, 6H), 3.57 (d, *J* = 15.4 Hz, 2H), 3.69 (d, *J* = 15.4 Hz, 2H), 6.48 (s, 2H), 6.94 (m, 4H), 6.99 (s, 4H), 7.10 (m, 2H), 7.21 (m, 6H), 7.29 (m, 6H), 7. 42 (m, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.9, 19.8, 31.5, 34.7, 36.8, 119.4, 123.4, 127.5, 127.7, 128.2, 128.7, 129.1, 129.8, 130.4, 130.9, 131.3, 134.3, 140.2, 150.1; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 109.45; HRMS (ESI+) calcd for $C_{70}H_{81}O_2P_2$ $[M + H]^+$ 1015.5712, found 1015.5728 (Δ = 1.6 ppm).

(*S*)-2,2′-Bisdiphenylphosphinoxy-3,3′-bis(2,6-diethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*S*)-L1d): white foam; 267 mg; yield 74%; mp 80−82 °C; $[\alpha]^{21}_D$ +125.8 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.5 Hz, 12H), 1.81 (s, 6H), 1.84 (s, 6H), 2.45 (q, *J* = 7.5 Hz, 8H), 3.58 (d, *J* = 16.9 Hz, 2H), 3.81 (d, *J* = 16.9 Hz, 2H), 6.08 (s, 2H), 7.07 (d, *J* = 7.6 Hz, 4H), 7.21 (s, 14H), 7.41 (m, 8H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 15.3, 16.6, 20.0, 26.3, 29.0, 126.0, 126.3, 127.7, 127.9, 128.4, 128.7, 129.0, 130.2, 130.3, 131.4, 134.0, 135.8, 143.2, 151.6; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 108.84; HRMS (ESI+) calcd for $C_{62}H_{65}O_2P_2$ $[M + H]^+$ 903.4460, found 903.4478 (Δ = 2.0 ppm).

(*S*)-2,2′-Bisdiphenylphosphinoxy-3,3′-bis(2-methylnaphthalen-1-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*S*)-L1g): white foam; 287 mg; yield 78%; mp 109−111 °C; $[\alpha]^{21}_D$ +106.2 (*c* 0.65, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 6H), 1.75 (s, 6H), 2.31 (s, 6H), 4.06 (d, *J* = 16.8 Hz, 2H), 4.17 (d, *J* = 16.8 Hz, 2H), 6.04 (s, 2H), 7.06 (m, 4H), 7.13 (m, 2H), 7.35 (m, 16H), 7.52 (m, 4H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.82 (m, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.8, 19.9, 20.5, 29.4, 124.5, 124.7, 125.9, 126.4, 127.9, 128.2, 128.8, 129.0, 129.7, 129.8, 130.3, 130.4, 131.6, 132.4, 133.0, 133.8, 134.4, 134.5, 143.2, 151.5; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 110.15; HRMS (ESI+) calcd for $C_{64}H_{57}O_2P_2$ $[M + H]^+$ 919.3834, found 919.3842 (Δ = 0.9 ppm).

(*S*)-2,2′-Bisdiphenylphosphinoxy-3,3′-bis(2-isopropylnaphthalen-1-ylmethyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*S*)-L1h): white foam; 277 mg; yield 71%; mp 106−108 °C; $[\alpha]^{21}_D$ +162.2 (*c* 0.37, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.8 Hz, 6H), 1.27 (d, *J* = 6.8 Hz, 6H), 1.73 (s, 6H), 1.78 (s, 6H), 3.26 (m, 2H), 4.12 (d, *J* = 17.1 Hz, 2H), 4.26 (d, *J* = 17.1 Hz, 2H), 6.13 (s, 2H), 7.09 (m, 4H), 7.16 (m, 2H), 7.29 (m, 6H), 7.39 (m, 4H), 7.52 (m, 10H), 7.81 (m, 4 H), 7.88 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.7, 19.9, 23.8, 23.9, 28.6, 29.6, 123.8, 124.6, 125.3, 125.9, 127.0, 127.9, 128.1, 128.7, 129.0, 129.4, 129.7, 130.3, 131.5, 131.9, 132.2, 133.0, 134.4, 143.2, 144.5, 151.2; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 109.95; HRMS (ESI+) calcd for $C_{68}H_{65}O_2P_2$ $[M + H]^+$ 975.4460, found 975.4490 (Δ = 3.1 ppm).

(*S*)-2,2′-Bis[bis(*p*-tolyl)phosphinoxy]-3,3′-bis(2,4,6-trimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*S*)-L2e): white foam; 290 mg; yield 78%; mp 110−112 °C; $[\alpha]^{21}_D$ +119.4 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 6H), 1.87 (s, 6H), 2.07 (s, 12H), 2.28 (s, 6H), 2.32 (s, 6H), 2.33 (s, 6H), 3.54 (d, *J* = 16.8 Hz, 2H), 3.70 (d, *J* = 16.8 Hz, 2H), 6.12 (s, 2H), 6.87 (s, 4H), 7.01 (d, *J* = 7.8 Hz, 4H), 7.06 (d, *J* = 7.8 Hz, 4H), 7.32 (m, 8H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.7, 19.9, 20.9, 21.3, 21.3, 29.9, 128.0, 128.5, 128.6, 129.4, 130.3, 130.5, 131.2, 134.1, 134.5, 135.0, 137.2, 138.2, 138.6, 152.0; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 110.40; HRMS (ESI+) calcd for $C_{64}H_{69}O_2P_2$ $[M + H]^+$ 931.4773, found 931.4798 (Δ = 2.7 ppm).

(*S*)-2,2′-Bis[bis(*m*-xylyl)phosphinoxy]-3,3′-bis(2,4,6-trimethylbenzyl)-5,5′,6,6′-tetramethyl-1,1′-biphenyl ((*S*)-L3e): white foam; 296 mg; yield 75%; mp 114−116 °C; $[\alpha]^{21}_D$ +104.8 (*c* 0.21, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 6H), 1.83 (s, 6H), 2.03 (s, 12H), 2.20 (s, 12H), 2.22 (s, 12H), 2.27 (s, 6H), 3.43 (d, *J* = 16.6 Hz, 2H), 3.71 (d, *J* = 16.4 Hz, 2H), 6.10 (s, 2H), 6.82 (s, 4H), 6.83 (s, 4H), 7.04 (s, 4H), 7.08 (s, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.6, 19.9, 20.8, 21.3, 21.4, 29.6, 126.8, 127.8, 128.2, 128.5, 130.3, 130.5, 130.9, 133.9, 134.8, 135.0, 136.8, 136.9, 137.1, 151.9; ^{13}P NMR (121.5 Hz, $CDCl_3$) δ 111.25; HRMS (ESI+) calcd for $C_{68}H_{77}O_2P_2$ $[M + H]^+$ 987.5399, found 987.5406 (Δ = 0.7 ppm).

2-*tert*-Butyldiphenylsiloxymethylcyclohex-2-enyl Ethenyl Carbonate (7c). A solution of 2-hydroxymethyl-2-cyclohexenol[30] (1.28 g, 10 mmol), *tert*-butyldiphenylsilyl chloride (2.8 g, 10 mmol), and imidazole (2 g, 30 mmol) in THF (16 mL) was stirred at 0 °C for 1.5 h. Then AcOEt (50 mL) was added, and the organic layer was washed with water (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 6:1) to afford 2-*tert*-butyldiphenylsiloxymethyl-2-cyclohexenol (3.29 g, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.58 (m, 1H), 1.78 (m, 4H), 2.08 (m, 1H), 2.86 (s, 1H), 4.20 (d, *J* = 11.9 Hz, 1H), 4.31 (m, 2H), 5.70 (brs, 1H), 7.42 (m, 6H), 7.73 (d, *J* = 7.4 Hz, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 17.8, 19.1, 25.2, 26.8, 31.0, 66.0, 68.3, 127.2, 127.7, 127.7, 129.7, 129.7, 133.0, 133.0, 135.6, 135.6, 137.2; HRMS (ESI+) calcd for $C_{23}H_{31}O_2Si$ $[M + H]^+$ 367.2093, found 367.2103 (Δ = 2.7 ppm).

To a solution of 2-*tert*-butyldiphenylsiloxymethyl-2-cyclohexenol (2.9 g, 8.0 mmol) and pyridine (7 mL) in CH_2Cl_2 (24 mL) was added vinyl chloroformate (0.7 mL, 8.0 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexanes/AcOEt = 30:1) to afford **7c** (3.2 g, 91%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.74 (m, 3H), 2.08 (m, 3H), 4.10 (d, *J* = 12.8 Hz, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 4.56 (dd, *J* = 1.9, 6.2 Hz, 1H), 4.90 (dd, *J* = 1.9, 13.9 Hz, 1H), 5.37 (brs, 1H), 5.97 (brs, 1H), 7.10 (dd, *J* = 6.2, 13.9 Hz, 1H), 7.40 (m, 6H), 7.67 (d, *J* = 7.0 Hz, 4H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 17.6, 19.1, 24.7, 26.7, 28.2, 64.9, 71.7, 97.3, 127.5, 127.6, 129.5, 129.5, 129.5, 133.3, 133.4, 133.5, 135.4, 135.5, 142.6, 154.3; HRMS (ESI+) calcd for $C_{26}H_{32}O_4SiNa$ $[M + Na]^+$ 459.1968, found 459.1971 (Δ = 0.7 ppm).

(−)-2-Bromo-3-(2-(*tert*-butyldiphenylsiloxymethyl)cyclohex-2-enyloxy)-4-methoxybenzaldehyde ((−)-8c). A solution of **7c** (105 mg, 0.24 mmol) in DMF (1 mL) was added to a solution of **1** (46 mg, 0.20 mmol), $[Pd(allyl)Cl]_2$ (3.6 mg 5 mol %), and (*S*)-**L3e** (30 mg, 15 mol %) in DMF (1 mL) at 0 °C, which was preincubated for 15 min. The solution was allowed to stir at the same temperature for 36 h. The reaction mixture was diluted with diethyl ether and washed with water (3 × 10 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes/AcOEt = 20:1) to afford (−)-**8c** (112 mg, 97%) as a colorless oil: $[\alpha]^{21}_D$ −59.8 (*c* 0.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.56 (m, 2H), 2.12 (m, 4H), 3.66 (s, 3H), 4.35 (d, *J* = 13.8 Hz, 1H), 4.43 (d, *J* = 13.8 Hz, 1H), 4.81 (brs, 1H), 6.10 (brs, 1H), 6.85 (d, *J* = 8.4, 1H), 7.37 (m, 6H), 7.67 (m, 5H), 10.25 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 18.1, 19.3, 25.1, 26.9, 28.3, 55.7, 65.4, 75.7, 110.7, 123.5, 125.7, 127.3, 127.5, 127.6, 127.6, 129.5, 129.5, 133.7, 133.9, 135.5, 135.6, 135.6, 144.8, 158.4, 191.4; HRMS (ESI+) calcd for $C_{31}H_{36}O_4SiBr$ $[M + H]^+$ 579.1566, found 579.1561 (Δ = −0.9 ppm).

In a similar manner, allylic etherification products, (+)-**8a** and (+)-**8b**, were obtained using (*R*)-L**1f** as the chiral ligand.

(+)-2-Bromo-3-(2-(*tert*-butyldimethylsiloxymethyl)cyclohex-2-enyloxy)-4-methoxybenzaldehyde ((+)-8a): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.90 (s, 9H), 1.55 (m, 2H), 2.08 (m, 4H), 3.92 (s, 3H), 4.35 (brs, 2H), 4.88 (brs, 1H), 6.03 (brs, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −5.2, 18.1, 18.4, 25.1, 25.9, 28.2, 56.0, 64.5, 75.6, 110.7, 123.6, 125.7, 127.1, 127.5, 136.2, 144.7, 158.5, 191.5; HRMS (ESI+) calcd for $C_{21}H_{31}O_4SiBr$ $[M]^+$ 454.1175, found 454.1179 (Δ = 0.8 ppm).

(+)-2-Bromo-4-methoxy-3-(2-(triisopropylsiloxymethyl)-cyclohex-2-enyloxy)benzaldehyde ((+)-8b): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, *J* = 7.6 Hz, 18H), 1.10 (m, 3H), 1.59 (m, 2H), 2.02 (m, 3H), 2.22 (m, 1H), 3.92 (s, 3H), 4.38 (d, *J* = 13.9 Hz, 1H), 4.48 (d, *J* = 13.9 Hz, 1H), 4.85 (brs, 1H), 6.09 (brs, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 10.28 (s, 1H);

dx.doi.org/10.1021/jo400355j | *J. Org. Chem.* 2013, 78, 4013−4018

^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 17.7, 18.0, 25.1, 28.3, 55.9, 64.6, 75.8, 110.7, 123.7, 125.7, 126.4, 127.6, 136.1, 144.7, 158.5, 191.5; HRMS (ESI+) calcd for $C_{24}H_{37}O_4SiBr$ $[M]^+$ 496.1644, found 496.1645 (Δ = 0.2 ppm).

(−)-2-Bromo-3-(2-hydroxymethylcyclohex-2-enyloxy)-4-methoxybenzaldehyde ((−)-10). To a solution of (−)-**8c** (90 mg, 0.16 mmol) in THF (1.6 mL) was added tetra-*n*-butylammonium fluoride (1 M in THF, 0.2 mL) dropwise at room temperature. The mixture was stirred at the same temperature for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexanes/AcOEt = 2:1) to afford (−)-**10** (54 mg, 99%) as a white solid: $[\alpha]^{21}_D$ −106.5 (*c* 0.40, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50 (m, 2H), 2.03 (m, 3H), 2.24 (m, 1H), 3.98 (s, 3H), 4.27 (d, *J* = 12.4 Hz, 1H), 4.38 (d, *J* = 12.4 Hz, 1H), 4.95 (t, *J* = 4.1 Hz, 1H), 6.04 (brs, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.5, 25.2, 28.2, 56.3, 65.9, 77.3, 110.9, 124.0, 126.2, 127.8, 130.5, 136.3, 144.2, 158.1, 191.2. Enantiomers were separated by HPLC using Chiralcel OJ column eluting with 95:5 hexanes/2-propanol at 0.8 mL/min. Retention times: major enantiomer 55.1 min and minor 66.8 min. ^{1}H NMR and ^{13}C NMR data are in agreement with the literature values.[18]

(−)-(*S*)-2-Bromo-3-(2-cyanomethylcyclohex-2-enyloxy)-4-methoxybenzaldehyde (5). To a solution of (−)-**10** (41 mg, 0.12 mmol) and TEA (0.04 mL, 0.29 mmol) in CH_2Cl_2 (1 mL) was added methanesulfonyl chloride (0.013 mL, 0.17 mmol), and the solution was stirred at 0 °C for 15 min. The reaction mixture was then concentrated in vacuo. The residue was dissolved in ether and filtered through a pad of Celite. The filtrate was concentrated again. Because the crude product was unstable and prone to decomposition, it was immediately used for the next step without further purification.

To a solution of the previous crude product in DMSO (1 mL) was added NaCN (11.8 mg, 0.24 mmol), and the solution was stirred at room temperature for 1 h. Then EtOAc was added, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexanes/AcOEt = 5:1) to afford **5** (30 mg, 71% over two steps) as a white solid: $[\alpha]^{21}_D$ −81.0 (*c* 0.30, CH_2Cl_2) (97% ee based on optical rotation; lit.[18] $[\alpha]_D$ −80.0 (*c* 3.05, CH_2Cl_2), 96% ee); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (m, 2H), 2.01 (m, 3H), 2.25 (m, 1H), 3.35 (d, *J* = 18.1 Hz, 1H), 3.53 (d, *J* = 17.1 Hz, 1H), 3.99 (s, 3H), 4.82 (t, *J* = 3.5 Hz, 1H), 6.15 (brs, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 10.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 22.7, 25.4, 28.0, 56.2, 76.1, 111.0, 118.4, 123.6, 126.4, 127.0, 127.6, 132.9, 143.9, 158.2, 191.1. All data are in agreement with the literature values.[18]

(−)-1-Formyl-4-methoxy-6,7-dihydro-5a*H*-9a-cyanomethyldibenzofuran (6). To a 10 mL of flask were added **5** (30 mg, 0.08 mmol), $Pd(OAc)_2$ (2.9 mg, 0.012 mmol), Ag_2CO_3 (70.9 mg, 0.24 mmol), and dppp (5.3 mg, 0.012 mmol). Degassed toluene (1 mL) was added. and the resulting suspension was heated at 107 °C for 24 h. Direct column chromatography on silica gel (hexanes/AcOEt = 5:1) afforded (−)-**6** (19 mg, 90%) as a colorless liquid: $[\alpha]^{21}_D$ −201.0 (*c* 0.30, CH_2Cl_2) (lit.[18] $[\alpha]_D$ −199.0 (*c* 1.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (m, 2H), 2.22 (m, 1H), 2.38 (m, 1H), 3.13 (d, *J* = 17.0 Hz, 1H), 3.45 (d, *J* = 17.0 Hz, 1H), 3.97 (s, 3H), 4.97 (t, *J* = 3.4 Hz, 1H), 5.98 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 23.5, 26.1, 48.2, 56.2, 86.3, 111.0, 117.4, 126.0, 126.5, 130.5, 130.6, 132.0, 148.9, 150.3, 191.6. All data are in agreement with the literature values.[18]

■ 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: iwao.ojima@stonybrook.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant from the National Science Foundation.

■ REFERENCES

(1) Hoshino, O. *Alkaloids (Academic Press)* **1998**, *51*, 324.
(2) Martin, S. F. *Alkaloids (Academic Press)* **1987**, *30*, 251.
(3) Marco-Contelles, J.; Carreiras, M. d. C.; Rodriguez, C.; Villarroya, M.; Garcia, A. G. *Chem. Rev. (Washington, DC, U.S.)* **2006**, *106*, 116.
(4) Nordberg, A.; Svensson, A.-L. *Drug Saf.* **1998**, *19*, 465.
(5) Lilienfeld, S. *CNS Drug Rev.* **2002**, *8*, 159.
(6) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806.
(7) Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463.
(8) Guillou, C.; Beunard, J.-L.; Gras, E.; Thal, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 4745.
(9) Hu, X.-D.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.-A.; Wang, M. *Org. Lett.* **2006**, *8*, 1823.
(10) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498.
(11) Kodama, S.; Hamashima, Y.; Nishide, K.; Node, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2659.
(12) Satcharoen, V.; McLean, N. J.; Kemp, S. C.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2007**, *9*, 1867.
(13) Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc.* **2009**, *131*, 16045.
(14) Chida, N.; Kato, T.; Yamada, H. *Heterocycles* **2010**, *82*, 563.
(15) Kueenburg, B.; Czollner, L.; Froehlich, J.; Jordis, U. *Org. Process Res. Dev.* **1999**, *3*, 425.
(16) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262.
(17) Trost, B. M.; Tang, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2795.
(18) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785.
(19) Chen, P.; Bao, X.; Zhang, L.-F.; Ding, M.; Han, X.-J.; Li, J.; Zhang, G.-B.; Tu, Y.-Q.; Fan, C.-A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8161.
(20) Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 2714.
(21) Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831.
(22) Hua, Z.; Vassar, V. C.; Choi, H.; Ojima, I. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5411.
(23) Choi, H.; Hua, Z.; Ojima, I. *Org. Lett.* **2004**, *6*, 2689.
(24) Chapsal, B. D.; Hua, Z.; Ojima, I. *Tetrahedron: Asymmetry* **2006**, *17*, 642.
(25) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395.
(26) Shi, C.; Ojima, I. *Tetrahedron* **2007**, *63*, 8563.
(27) Shi, C.; Chien, C.-W.; Ojima, I. *Chem. Asian J.* **2011**, *6*, 674.
(28) Lin, C.-F.; Ojima, I. *J. Org. Chem.* **2011**, *76*, 6240.
(29) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(30) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801.
(31) Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110.