

## Aminobromination of Unsaturated Phosphonates

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**Abstract:** Unexpected *syn*  $\beta$ -amino- $\alpha$ -bromination of unsaturated phosphonates was observed under typical Sharpless AA reaction conditions with excess *N*-bromoacetamide.

The synthesis of  $\alpha$ - and/or  $\beta$ -substituted phosphonic acids is an important area of research, particularly in connection with the search for a biologically active surrogate for the corresponding carboxylic acids and phosphoric acids. Interesting inhibitory activities toward renin and HIV protease have been observed with phosphonic acid derivatives.<sup>1</sup> The syntheses of both racemic and optically active phosphonates have been reported. Recently, the Sharpless<sup>2</sup> and Sisti<sup>3</sup> groups have applied the asymmetric aminohydroxylation (AA) reaction described by Sharpless et al.<sup>4</sup> to unsaturated phosphonates to afford vicinal aminohydroxyl groups using osmium and cinchona alkaloid ligands in low to moderate yields.

In our previous paper,<sup>5</sup> we demonstrated the asymmetric syntheses of  $\alpha$ -substituted- $\beta$ -amino acid derivatives utilizing the nucleophilic ring-opening reaction of both *cis*- and *trans*-oxazoline-5-carboxylates. These oxazoline-5-carboxylates were easily prepared from *syn*-acetyl amino alcohols, which can be obtained via the acetamide-based Sharpless AA reaction using  $\alpha,\beta$ -unsaturated carboxylates as starting materials. To extend this oxazoline ring-opening methodology for the preparation of  $\alpha$ -substituted  $\beta$ -amino phosphonates, we attempted to use the acetamide-based Sharpless AA

reaction using  $\alpha,\beta$ -unsaturated phosphonates as substrates. In the course of probing the reaction conditions, we observed the novel *syn*- $\beta$ -amino- $\alpha$ -bromination of electron-rich unsaturated phosphonates where *N*-bromoacetamide was used as the nitrogen/bromine sources.

In the Sharpless AA reactions with vinyl phosphonates,<sup>2</sup> the corresponding *N*-chloro-*N*-sodioamides were used as nitrogen sources to introduce *N*-*p*-toluenesulfonyl and ethoxycarbonyl amino groups. The yields of  $\beta$ -amino- $\alpha$ -hydroxy phosphonates varied from 21 to 53% depending on the starting materials. In addition, the formation of diols and regioisomers was reported under these reaction conditions. In our case, *N*-bromoacetamide was used as the nitrogen source following a typical AA procedure for cinnamate ester<sup>4c</sup> to prepare the corresponding aminohydroxylation product from the vinyl phosphonate **1**. However, in our initial attempt using 1.1 equiv of *N*-bromoacetamide, no starting material **1** was consumed in the presence of different kinds of 1:1 aqueous solvents such as *tert*-butyl alcohol, 1-propanol, and acetonitrile and a prolonged reaction time (2 days), although the color of the reaction mixture changed from green to light yellow in all cases. Once 3.5 equiv of *N*-bromoacetamide was added, all of the starting vinyl phosphonate disappeared within 2 h and we observed an unexpected *syn*- $\beta$ -amino- $\alpha$ -bromination product instead of aminohydroxylation product (Scheme 1).

The identification of the unexpected product **2** was first revealed via MS spectroscopy in which a prominent molecular ion peak at 436.0888 (*M* + *H*) accompanied by a 438.0870 peak (*M* + *H* + 2) with an almost equal intensity supported the presence of an aminobromination product rather than the anticipated aminohydroxylation product at 374. In addition, the presence of the [MeOPhCHNHCOCH<sub>3</sub>]<sup>+</sup> fragment ion peak at 178 and the absence of the [MeOPhCHBr]<sup>+</sup> fragment ion peak at 199 and 201 showed the  $\beta$ -amino- $\alpha$ -bromo regioselectivity. This regiochemistry was further characterized by <sup>1</sup>H–<sup>1</sup>H COSY analysis of the diisopropyl phosphonate **2** as follows: While the sextet peak at 5.60 ppm showed strong correlations with both the amide group (6.50 ppm) and the peak at 4.09 ppm and weak correlation with aryl protons (7.21 ppm), the doublet–doublet peak at 4.09 ppm with a coupling constant of 12.2 Hz had only one correlation with the sextet peak and should be more likely to belong to the C-1 proton, which attached to the same carbon atom with a bromine atom. <sup>1</sup>H–<sup>13</sup>C HMQC 2D NMR analysis confirmed this interpretation that the carbon atom correlating with the proton at 4.09 ppm has a chemical shift of 49 ppm and a distinct geminal phosphorus–carbon coupling constant of 153 Hz.

Although the alcoholic solvents (*tert*-butyl alcohol and 1-propanol) or acetonitrile were commonly used in Sharpless AA reactions,<sup>2,4</sup> a much simpler reaction mixture was obtained using acetonitrile in our case. The amount of *N*-bromoacetamide was also an important factor; further experiments revealed that more than 2.0 equiv of acetamide was necessary while reducing the amount of the acetamide to 1.6 equiv significantly retarded the reactiv-

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## SCHEME 1. Unexpected Aminobromination of Unsaturated Phosphonate

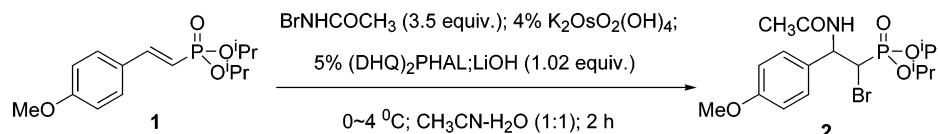


TABLE 1. Results of the Aminobromination of Aryl-Substituted Unsaturated Phosphonate Diesters

Entry	Substrate	Isolated Product	Yield <sup>a</sup>
1			26 % (19%) [(DHQ) <sub>2</sub> PHAL]
			25 % (18%) [(DHQD) <sub>2</sub> PHAL]
2			29% (21%) [(DHQ) <sub>2</sub> PHAL]
			28% (21%) [(DHQD) <sub>2</sub> PHAL]
3			35%[(DHQ) <sub>2</sub> PHAL]
			30%[(DHQD) <sub>2</sub> PHAL]
4			24%[(DHQ) <sub>2</sub> PHAL]
			21%[(DHQD) <sub>2</sub> PHAL]

<sup>a</sup> The numbers in parentheses represent the yield after a single recrystallization (>99% purity as evidenced by <sup>31</sup>P NMR). Noncrystalline products **6** [(DHQ)<sub>2</sub>PHAL], **6** [(DHQD)<sub>2</sub>PHAL], **8** [(DHQ)<sub>2</sub>PHAL], and **8** [(DHQD)<sub>2</sub>PHAL] were isolated in 95, 89, 92, and 88% purity (as evidenced by <sup>31</sup>P NMR<sup>7</sup>), respectively.

ity of this reaction. There was no reaction in the absence of the osmium catalyst.

On the basis of this interesting result, various unsaturated aryl phosphonates with different substitution groups (R = phenyl, *p*-chlorophenyl, *o*-methoxyphenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, 3,4-dimethoxyphenyl, *p*-*N,N*-dimethylaminophenyl, *p*-tolyl, 2-furyl, 3-furyl, *p*-nitrophenyl, and naphthyl), prepared using a modified Horner–Wittig reaction,<sup>6</sup> were subjected to the same conditions to investigate the applicability of this reaction. Among the vinyl phosphonates examined, only electron-

rich and para-substituted 2-phenyl vinyl phosphonates (R = *p*-methoxyphenyl, 3,4-dimethoxyphenyl, and *p*-*N,N*-dimethylaminophenyl) gave β-amino-α-bromo phosphonates (Table 1). On the other hand, only starting material or hydrolysis products were obtained from the rest of the vinyl phosphonates under the same reaction conditions. The yields of β-amino-α-bromo phosphonates varied from 21% to 35%. The main byproduct was the corresponding *syn*-β-hydroxy-α-brominated adduct in most cases.<sup>7</sup>

To assign the stereochemistry of the β-amino-α-bromophosphonates and confirm the regiochemistry aforementioned, a suitable single crystal of compound **4** was submitted for X-ray crystal determination. The X-ray structure (see the Supporting Information) confirmed the *syn* stereochemistry and regiochemistry.

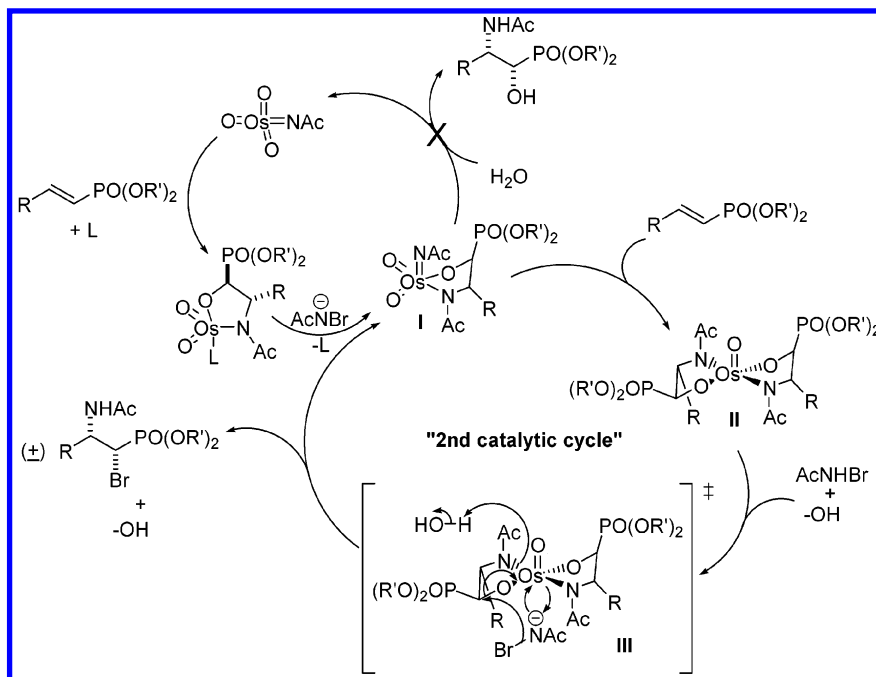
However, most surprisingly, almost no enantioselectivity was observed in our reactions using (DHQ)<sub>2</sub>PHAL or (DHQD)<sub>2</sub>PHAL as a chiral ligand. Changes in the addition sequence, the amount of base (0.5 equiv), or the amount of potassium osmate dihydrate (0.02 or 0.08

(6) Rambaud, M.; Vecchio, A.; Villieras, J. *Synth. Commun.* **1984**, *14*, 833.

(7) The β-hydroxy-α-bromo regiochemistry of the hydroxybrominated adduct was determined using the MS spectroscopy and <sup>1</sup>H NMR coupling constants by an analysis similar to that used in the identification of our β-amino-α-brominated adduct. The *syn* stereoselectivity was determined as follows: the epoxide was synthesized from diethyl [1-bromo-2-hydroxy-2-(*p*-methoxyphenyl)ethyl]phosphonate and the latter was confirmed as a *cis* isomer based on the coupling constants in <sup>1</sup>H NMR spectrum. The *J*<sub>P-H</sub> and *J*<sub>H-H</sub> of hydrogen at the C-2 position (*CHP*) were 28.13 and 4.47 Hz, respectively, which were consistent with 28.24 and 4.49 Hz in (±)-*cis*-diethyl 1,2-epoxy-2-phenylethylphosphonate. (a) Cristau, H. J.; Yangkou-Mbianda, X.; Geze, A.; Beziat, Y.; Gasc, M. B. *J. Organomet. Chem.* **1998**, *571*, 189. (b) Cristau, H. J.; Pirat, J.-L.; Drag, M.; Kafarski, P. *Tetrahedron Lett.* **2000**, *41*, 9781. The detailed results and mechanism will appear elsewhere. However, we believe the mechanistic pathway for the formation of this *syn*-β-hydroxy-α-brominated adduct might be similar to that of our *syn*-β-amino-α-brominated adduct and closely related to the formation of commonly observed dihydroxylated side products in the Sharpless AA reactions.

(8) The noncrystalline products were always accompanied by small amounts of phosphorous byproducts as shown by <sup>31</sup>P NMR. Similar phenomena were previously reported.<sup>1,6b</sup> No further attempts were made to identify these compounds in this paper.

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SCHEME 2. Proposed Mechanism for the Aminobromination Reaction<sup>a</sup>

<sup>a</sup> L = ligand.

mmol) did not help to increase the ee, even though there were discernible differences in the distribution of the products.

Recently, Li et al. reported a novel *anti*- $\alpha$ -amino- $\beta$ -halogenation of cinnamic esters using *N,N*-dichloro-*p*-toluenesulfonamide as the chlorine/nitrogen sources.<sup>9</sup> In their reports, *N*-tosyl-*N*-chloroaziridinium was proposed as a possible intermediate to explain the regio- and stereochemical outcome. Also, a recent report from the Sudalai group<sup>10</sup> illustrated the transition-metal-catalyzed regio- and stereoselective aminobromination of olefins with TsNH<sub>2</sub> and NBS as the nitrogen and bromine sources, respectively. *anti*- $\beta$ -Amino- $\alpha$ -bromo adducts were mainly obtained in this case via the bromonium ion intermediate.

On the contrary, the fact that we obtained only *syn*- $\beta$ -amino- $\alpha$ -brominated phosphonates under our reaction conditions clearly excludes the involvement of aziridinium or bromonium intermediate. To explain the regio- and stereoselectivity of the resulting *syn*- $\beta$ -amino- $\alpha$ -brominated phosphonates, a catalytic pathway is proposed as shown in Scheme 2. Possibly, in our cases, the second catalytic cycle illustrated in the Sharpless paper<sup>3b</sup> was promoted so that both enantiomers were produced. After the first olefin substitution, the second olefin may be promoted to bind to osmium to go to the ligand-independent second cycle of reaction under our reaction conditions. The osmium(VI) bisazaglycolates (II, Scheme 2) are supposed to be attacked by *N*-bromoacetamide anion during the reoxidation process in our case. Concomitantly, the releasing bromides attack at the  $\alpha$ -position of glycolates from the osmium side to produce the *syn*- $\beta$ -amino- $\alpha$ -brominated phosphonates.

In conclusion, we demonstrated a new  $\beta$ -amino- $\alpha$ -bromination of unsaturated phosphonates under typical

Sharpless AA reaction condition with excess *N*-bromoacetamide as the nitrogen/bromine sources. Attempts to vary the primary amide, by using amides other than acetamide, to elucidate the reaction mechanism and an effort to increase the yield and ee of this aminobromination reaction are currently in progress.

## Experimental Section

**General Procedure for Aminobromination Reaction of Vinyl Phosphonates.** To a magnetically stirred solution of vinyl phosphonate (1 mmol) and 39 mg of (DHQ)<sub>2</sub>PHAL or (DHQD)<sub>2</sub>PHAL ligand (0.05 mmol) in 7 mL of acetonitrile were added water (7 mL), LiOH·H<sub>2</sub>O (42.8 mg, 1.02 mmol), and potassium osmate dihydrate (14.7 mg, 0.04 mmol) to afford a pale pinkish solution. After 10 min of stirring in an ice–water bath, *N*-bromoacetamide (320 mg, 2.3 mmol) was added in one portion which caused the color of the reaction mixture to change to green immediately. With vigorous stirring, the color gradually changed to yellow during 30 min. The reaction was monitored by TLC (EtOAc/hexane = 3:1). (A change in color to clear yellow did not always mean the consumption of the olefin starting materials. When 1.1 equiv of *N*-bromoacetamide was used, the reaction mixture also changed to yellow with all of the olefin remaining as shown by TLC). After the end of the reaction, sodium sulfite (500 mg) was added, the mixture was stirred for another 1 h at room temperature, and ethyl acetate (10 mL) was added. The aqueous phase was then extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. After concentration in vacuo, the crude residue was purified first by flash chromatography (1% MeOH/EtOAc) to remove most of the side product and then by preparative TLC with 2% MeOH/chloroform to afford the aminobromination product.

**Diisopropyl [2-Acetylamino-1-bromo-2-(*p*-methoxyphenyl)ethyl]phosphonate (2).** A yield of 114 mg (0.262 mmol, 26%) of crude white solid was obtained with (DHQ)<sub>2</sub>PHAL. After recrystallization with EtOAc/hexane, 81 mg (0.187 mmol, 19%) of white, fluffy, crystalline solid was obtained: mp 152–3 °C; IR (KBr) 3415, 2952, 2926, 2852, 1663, 1610 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  1.08 (d, *J* = 6.2 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.34–1.40 (m, 6H), 2.09 (s, 3H), 3.79 (s, 3H), 4.09 (dd,

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$J = 2.6, 12.2$  Hz, 1H), 4.77–4.83 (m, 2H), 5.60 (sextet,  $J = 2.5, 7.9$  Hz, 1H), 6.50 (d,  $J = 7.8$  Hz, 1H), 6.86 (d,  $J = 8.7$  Hz, 2H), 7.22 (d,  $J = 8.6$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  23.5, 23.8 (d,  $J = 6.1$  Hz), 24.0 (d,  $J = 5.7$  Hz), 24.4–24.7 (m), 49.0 (d,  $J = 153$  Hz), 51.9 (d,  $J = 1.6$  Hz), 55.5, 73.1 (d,  $J = 7.3$  Hz), 73.4 (d,  $J = 7.5$  Hz), 113.9, 127.8, 131.1 (d,  $J = 12.6$  Hz), 159.3, 169.5;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 202 MHz)  $\delta$  16.33; HRMS (FAB)  $m/z = 436.0888$   $[\text{M} + \text{H}]^+$  and 438.0870  $[\text{M} + 2 + \text{H}]^+$  (1:1), calcd for  $\text{C}_{17}\text{H}_{28}\text{BrNO}_5\text{P} = 436.0881$ . Anal. Calcd for  $\text{C}_{17}\text{H}_{27}\text{BrNO}_5\text{P}$ : C, 46.80; H, 6.24; N, 3.21. Found: C, 47.08; H, 6.32; N, 3.18.

A yield of 110 mg (0.252 mmol, 25%) of crude white solid was obtained with  $(\text{DHQD})_2\text{PHAL}$ . After recrystallization with EtOAc/hexane, 80 mg (0.183 mmol, 18%) of white, fluffy, crystalline solid was obtained.

**Diethyl [2-Acetylamino-1-bromo-2-(*p*-methoxyphenyl)ethyl]phosphonate (4).** A yield of 118 mg (0.29 mmol, 29%) of crude white solid was obtained with  $(\text{DHQ})_2\text{PHAL}$ . After recrystallization with EtOAc/hexane, 86 mg (0.21 mmol, 21%) of white crystalline solid was obtained: mp 116–7 °C; IR (KBr) 3279, 2983, 2927, 1659, 1611, 1514  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  1.32 (t,  $J = 14.1$  Hz, 3H), 1.38 (t,  $J = 14.1$  Hz, 3H), 2.10 (s, 3H), 3.80 (s, 3H), 4.13–4.21 (m, 2H), 4.21–4.24 (m, 3H), 5.63 (sextet,  $J = 2.6, 8.6$  Hz, 1H), 6.48 (d,  $J = 8.0$  Hz, 1H), 6.87 (d,  $J = 8.7$  Hz, 2H), 7.22 (d,  $J = 8.6$  Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  16.7, 23.6, 48.1 (d,  $J = 152$  Hz), 51.9, 55.5 (d,  $J = 4.0$  Hz), 64.2 (d,  $J = 6.8$  Hz), 64.5 (d,  $J = 6.8$  Hz), 114.1, 114.6, 127.9, 130.9, 159.5, 169.6;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 202 MHz)  $\delta$  18.24; HRMS (FAB)  $m/z$  408.0551  $[\text{M} + \text{H}]^+$  and 410.0551  $[\text{M} + 2 + \text{H}]^+$  (1:1), calcd for  $\text{C}_{15}\text{H}_{24}\text{BrNO}_5\text{P} = 408.0569$ . Anal. Calcd for  $\text{C}_{15}\text{H}_{23}\text{BrNO}_5\text{P}$ : C, 44.13; H, 5.68; N, 3.43. Found: C, 44.50; H, 5.69; N, 3.40.

The single crystal was grown in a NMR test tube during about 10 days with 0.2 mL of ethyl acetate and 2 mL of hexane.

A yield of 114 mg (0.28 mmol, 28%) of crude white solid was obtained with  $(\text{DHQD})_2\text{PHAL}$ . After recrystallization with EtOAc/hexane, 86 mg (0.211 mmol, 21%) of white crystalline solid was obtained.

**Diisopropyl [2-Acetylamino-1-bromo-2-(3',4'-dimethoxyphenyl)ethyl]phosphonate (6).** A yield of 144 mg (0.31 mmol, 31%) of a viscous, yellow oil with 5% impurities (by  $^{31}\text{P}$  NMR) was obtained with  $(\text{DHQ})_2\text{PHAL}$ : IR (KBr) 3293, 2981,

2937, 1660, 1595  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  1.31 (d,  $J = 6.2$  Hz, 3H), 1.34 (d,  $J = 6.2$  Hz, 3H), 1.38–1.40 (m, 6H), 2.09 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.11 (dd,  $J = 2.6, 12.2$  Hz, 1H), 4.78–4.83 (m, 2H), 5.58 (sextet,  $J = 2.4, 8.1$  Hz, 1H), 6.49 (d,  $J = 7.7$  Hz, 1H), 6.81–6.87 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  23.5, 23.9 (d,  $J = 5.9$  Hz), 24.0 (d,  $J = 5.6$  Hz), 24.4–24.5 (m), 48.9 (d,  $J = 153$  Hz), 52.3, 56.2, 56.3, 73.1 (d,  $J = 7.3$  Hz), 73.5 (d,  $J = 7.4$  Hz), 110.7, 111.3, 119.1, 131.7 (d,  $J = 12.3$  Hz), 149.0, 149.2, 169.5;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 202 MHz)  $\delta$  16.28; HRMS (FAB)  $m/z$  466.0994  $[\text{M} + \text{H}]^+$  and 468.0976  $[\text{M} + 2 + \text{H}]^+$  (1:1), calcd for  $\text{C}_{18}\text{H}_{30}\text{BrNO}_6\text{P} = 466.0986$ .

A yield of 140 mg (0.30 mmol, 30%) of a viscous, yellow oil with 11% impurities (by  $^{31}\text{P}$  NMR) was obtained with  $(\text{DHQD})_2\text{PHAL}$ .

**Diisopropyl [2-Acetylamino-1-bromo-2-(4'-*N,N*-dimethylaminophenyl)ethyl]phosphonate (8).** A yield of 107 mg (0.238 mmol, 24%) of a viscous, yellow oil with 8% impurity (by  $^{31}\text{P}$  NMR) was obtained with  $(\text{DHQ})_2\text{PHAL}$ :  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  1.26 (d,  $J = 7.4$  Hz, 3H), 1.32 (d,  $J = 6.6$  Hz, 3H), 1.34–1.38 (m, 6H), 2.09 (s, 3H), 2.78 (s, 6H), 4.06 (dd,  $J = 2.6, 12.2$  Hz, 1H), 4.76–4.82 (m, 2H), 5.52–5.55 (m, 1H), 6.52 (d,  $J = 7.6$  Hz, 1H), 7.02 (d,  $J = 8.1$  Hz, 1H), 7.18 (d,  $J = 8.3$  Hz, 1H), 7.48 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  23.5, 23.9 (d,  $J = 5.7$  Hz), 24.0 (d,  $J = 5.6$  Hz), 24.4–24.8 (m), 44.4, 48.2 (d,  $J = 153$  Hz), 51.9, 55.1, 73.2 (d,  $J = 7.0$  Hz), 73.6 (d,  $J = 7.2$  Hz), 119.2, 120.4, 126.7, 132.2, 151.7, 169.5;  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 202 MHz)  $\delta$  16.05; HRMS (FAB)  $m/z$  447.1033  $[\text{M} - \text{H}]^+$  and 449.1044  $[\text{M} + 2 - \text{H}]^+$  (1:1), calcd for  $\text{C}_{18}\text{H}_{29}\text{BrN}_2\text{O}_4\text{P} = 447.1040$ .

A yield of 96 mg (0.214 mmol, 21%) of a viscous, yellow oil with 12% impurities (by  $^{31}\text{P}$  NMR) was obtained with  $(\text{DHQD})_2\text{PHAL}$ .

**Acknowledgment.** We thank Professor Myung Ho Hyun for the chiral HPCL data. Financial support from the Brain Korea 21 Program is gratefully acknowledged.

**Supporting Information Available:** Data for the X-ray crystal structure of **4** ( $1R^*, 2S^*$ ). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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