The Catalytic Asymmetric Aminohydroxylation of Unsaturated Phosphonates

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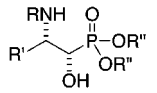
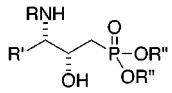
Introduction

Phosphonic acids with heteroatoms in the α and/or *β* positions have attracted much attention recently for their involvement in biologically relevant processes such as inhibition of renin[1] and HIV protease[2] and for their use as haptens in the development of catalytic antibodies.[3] Syntheses of both racemic and optically active phosphonates have been published.[4,5] The recently discovered asymmetric aminohydroxylation (AA),[6] which utilizes Os(VIII) and the cinchona alkaloid ligand $(DHQ)_2PHAL$ as catalysts, allows for formation of *β*-amino-α-hydroxyphosphonate diesters of type **I** in high ee.[7] A *γ*-aminohydroxyphosphonate containing an α-methylene moiety (type **II**) was similarly prepared albeit with lower enantioselectivity. Phosphonates such as **I** and **II** have resulted in unique phosphate mimics with resistance to phosphatase hydrolysis.[8]



I



II

Results and Discussion

Seven different unsaturated phosphonate substrates were examined (Table 1). Both the *p*-toluenesulfonyl (R = Ts) and ethoxycarbonyl (R = EtO_2C) *N*-amino groups were introduced via the corresponding *N*-chloro-*N*-sodioamides. Unfortunately, only aryl-substituted olefins (R′ = Ar) were successfully oxyaminated. The corresponding alkyl-substituted alkenes (e.g., R′ = H, methyl, *tert*-butyl, cyclohexyl) failed to react even upon prolonged heating.

The solvents, CH_3CN for sulfonamides and *n*-PrOH for carbamates, were not interchangeable. Use of *n*-PrOH resulted in higher ee's in both sulfonamide and carbamate AA products (e.g., **2a** was generated in 90% ee using *n*-PrOH). However, utilization of *n*-PrOH in the former resulted in lower isolated yields due to low conversion of olefin (e.g., 40% unreacted olefin after 24 h in forming **2a** using *n*-PrOH). Fortunately, it was discovered that the ee's of the hydroxysulfonamide products could be greatly enhanced by recrystallization. Several byproducts were formed during AA reactions (as analyzed by ^{31}P NMR), including some diol (5−25% of major isomer for sulfonamides and 15−30% for carbamates), and regioisomer (15−30% of major isomer for sulfonamides and 5−15% of major isomer for carbamates).[10] The amounts of regioisomer and diol present varied by substrate and with changes in reaction conditions. In addition, cleavage of the α-hydroxyphosphonate products to give an aldehyde and dialkyl phosphite was observed.[11] Thus, the

(1) (a) Dellaria, J. F., Jr.; Maki, R. G.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perun, T. J. *J. Med. Chem.* **1990**, *33*, 534. (b) Wester, R. T.; Chambers, R. J.; Green, M. D.; Murphy, W. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2005. (c) For reviews on phosphonates, see: Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. Dhawan, B.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119.

(2) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625.

(3) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234.

(4) (a) Smith, A. B., III.; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879. (b) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465. (c) Hanessian, S.; Bennani, Y. L. *Synthesis* **1994**, 1272. (d) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656. (e) Maury, C.; Gharbaoui, T.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 3687. (f) Demir, A. S.; Tanyeli, C.; Sesenoglu, O.; Demic, S. *Tetrahedron Lett.* **1996**, *37*, 407. (g) Meier, C.; Laux, W. H. G. *Tetrahedron* **1996**, *52*, 589. (h) Schmidt, U.; Oehme, G.; Krause, H. *Synth. Commun.* **1996**, *26*, 777. (i) Ferris, L.; Haigh, D.; Moody, C. J. *Synlett* **1995**, 921. (j) Tao, M.; Bihovsky, R.; Wells, G. J.; Mallamo, J. P. *J. Med. Chem.* **1998**, *41*, 3912.

(5) (a) Yokomatsu, T.; Yoshida, Y.; Suemune, K.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1995**, *6*, 365. (b) Yokomatsu, T.; Suemune, K.; Yamagishi, T.; Shibuya, S. *Synlett* **1995**, 847. (c) Kitamura, M.; Tokunaga, M.; Pham, T.; Lubell, W. D.; Noyori, R. *Tetrahedron Lett.* **1995**, *36*, 5769. (d) Zygmunt, J.; Gancarz, R.; Lejczak, B.; Wieczorek, P.; Kafarski, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2989. (e) Bongini, A.; Camerini, R.; Hofman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045. (f) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1995**, *38*, 4557. (g) Wroblewski, A. E.; Piotrowska, D. G. *Tetrahedron* **1998**, *54*, 8123.

(6) (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem.,Int. Ed. Engl.* **1996**, *35*, 451. (b) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813.

(7) We have recently been made aware that after our initial presentation of this work (Thomas, A. A.; Sharpless K. B. *Abstracts of Papers*; 213th National Meeting of the American Chemical Society, San Francisco, CA, Apr 13−17, 1997; American Chemical Society: Washington, DC, 1997; ORGN 126) another group published the preparation of α-hydroxy-*β*-toluenesulfonamidophosphonates by the AA: Cravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745.

(8) (a) Nieschalk, J.; Batsanov, A. S.; O'Hagan, D.; Howard, J. A. K. *Tetrahedron* **1996**, *52*, 165. (b) Burke, T. R., Jr.; Smyth, M. S.; Nomizu, M.; Otaka, A.; Roller, P. P. *J. Org. Chem.* **1993**, *58*, 1336.

(9) (a) Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *Synthesis* **1976**, 396. (b) For a review of vinylphosphonates, see: Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.

(10) Authentic, racemic diols of entries 1, 2, and 7 were prepared by a method similar to that of ref 11a. The ^{31}P chemical shift of diol relative to the corresponding hydroxysulfonamide (diol: $\Delta\delta_P = +1.3-1.9$ ppm) and hydroxycarbamate (diol: $\Delta\delta_P = +1.0-1.3$ ppm) products was assumed to be consistent within the series (with the exception of **7a** and **7b** in which $\Delta\delta_P$ for diol was +0.3 and +0.1 ppm, respectively). Authentic regioisomer (α-amino-*β*-hydroxyphosphonate) was not isolated for any of the entries. Correlation of ^1H NMR resonances for crude hydroxysulfonamide phosphonate products with those obtained from aminohydroxlation of unsaturated amides (Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637), in which both regioisomers were generated in high yield, allowed for identification of regioisomer in the former. With the exception of **7a** (see details below), the hydroxysulfonamide regioisomer was shifted downfield by 0.8−1.3 ppm in the ^{31}P NMR relative to the major isomer. Unfortunately, the assignment of regioisomer for the carbamates was less clear due to multiple, small resonances within the region of the ^{31}P NMR spectrum where the regioisomer was expected. Even though the carbamate regioisomer was not assigned, an upper limit of 15% (relative to major isomer) was set by integration of each of those small resonances in the ^{31}P NMR. Both ^1H and ^{13}C NMR spectra were too complicated to be useful in assessing the amount of regioisomer (or diol) present for the carbamates. The ^{31}P NMR for crude **7a** had numerous resonances (complicated by the fact that the starting olefin was not diasteromerically pure), and therefore, regioisomer assignments were not made.

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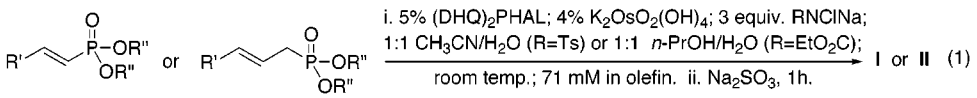
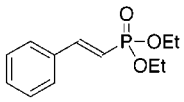
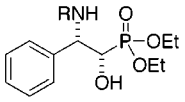
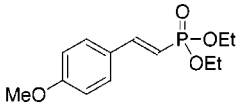
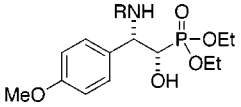
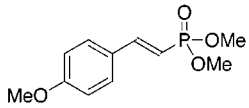
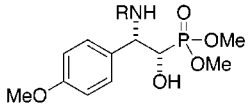
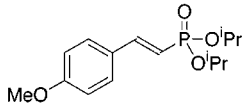
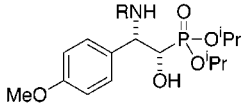
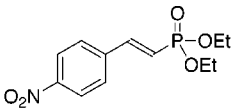
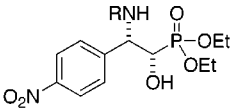
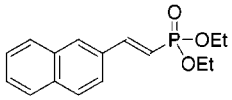
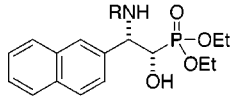
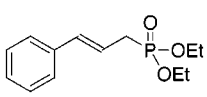
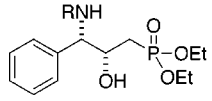
Table 1. Results of the AA of Aryl-Substituted, Unsaturated Phosphonate Diesters



Entry	Substrate[a]	Isolated Product[b]	R	Yield[c]	%ee[d]	t(h)[e]
1			**1a**: Ts	21	54 (91)	3
			1b: EtO_2C	32[f]	93	18
2			**2a**: Ts	31	76 (99)	3
			2b: EtO_2C	45	98 (99)	2
3			**3a**: Ts	35[f]	88	4
			3b: EtO_2C	32	98 (99)	1
4			**4a**: Ts	21	32[g]	4
			4b: EtO_2C	35	93 (99)	18
5			**5a**: Ts	40	92 (99)	12
			5b: EtO_2C	53[f]	97	4
6			**6a**: Ts	30	62 (93)	4
			6b: EtO_2C	53	98 (99)	2
7			**7a**: Ts	20	42 (94)	21
			7b: EtO_2C	29[f]	77 (90)[h]	4

[a] Unsaturated phosphonates were prepared using a modified Horner−Wittig reaction.[9] All of the olefins were >99% *E* configuration (as evidenced by ^1H or ^{31}P NMR) except for entry 7, which was used as an 89:11 ratio of *E*/*Z* isomers. [b] The stereochemistries depicted correspond to the known facial selectivity for the AA of cinnamate substrates[6] and the AD of entries 1 and 2.[5a] The regiochemistries were determined by 2D NMR analysis (details within). [c] Yields are of the isolated product from AA reactions after purification. Unless noted otherwise in the Experimental Section, the reactions were performed on a 2 or 0.5 mmol scale depending on whether the product was purified by recrystallization or preparative TLC, respectively. [d] The ee's were determined by HPLC analysis of both antipodes or by comparison with racemate using a chiracel AD column on crude reaction mixture or after purification by flash or thin-layer chromatography. The numbers in parentheses represent % ee after a single recrystallization and correspond with the yields listed in the table. [e] The reaction times were monitored by consumption of olefin as evidenced by TLC or ^{31}P NMR. [f] These noncrystalline products were purified exclusively by flash chromatography or preparative TLC. Products **3a** and **1b** were isolated in 87 and 90% purity, respectively, whereas **5b** and **7b** were of greater than 95% purity (as evidenced by ^{31}P NMR). [g] The value listed is the ee after preparative TLC; the racemate was obtained as a pure solid upon recrystallization from 2-propanol:THF (1:1). [h] Racemate crystallized leaving mother liquor that contained **7b** in 90% ee; the crude product was then purified by preparative TLC.

reaction times listed in Table 1 should be enforced; otherwise, poorer yields can be anticipated. Despite the subsequent low yields of AA products (Table 1), in almost all cases purity was high after recrystallization or preparative TLC.

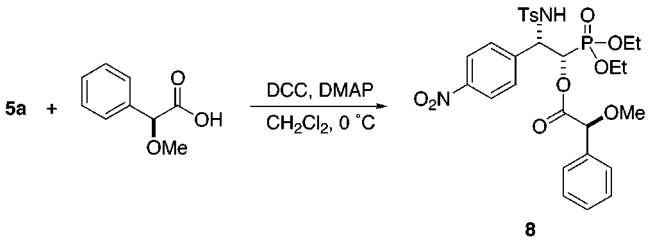
Purification of the AA phosphonate products was simplified by their dramatically increased retention on silica gel relative to remaining *p*-toluenesulfonamide or urethane. After removal of *p*-toluenesulfonamide or urethane by flash chromatography, the crude mixture was subsequently purified by recrystallization or preparative TLC. As mentioned above, the ee's of the sulfonamide products were generally lower than the corresponding carbamates; however, the sulfonamide products had the advantage of easier isolation, as most were readily purified by recrystallization. On the other hand, the carbamyl protecting group has the advantage of deprotection under milder conditions than the sulfonyl group.[12] It is expected that under typical acid-promoted deprotection of either the sulfonyl or carbamyl N-protecting groups, the phosphonate ester groups would also be removed. This is advantageous in cases where an aminophosphonic acid is the desired product. In other cases, however, orthogonal protecting groups are necessary. For the related cinnamates, it has been demonstrated that a variety of N-protecting groups are compatible with the AA.[13] We are currently exploring the scope of nitrogen sources possible in the AA of these vinyl phosphonates.[14]

To elucidate the regiochemistry of the phosphonate AA products, **7b** was subjected to $^1H-^1H$ COSY and $^1H-^{13}C$ HETCOR 2D NMR analysis (see the Supporting Information). In conjuction with the 2D NMR analysis, ^{13}C NMR revealed a distinct geminal phosphorus−carbon coupling constant of 139 Hz as expected for the methyl-

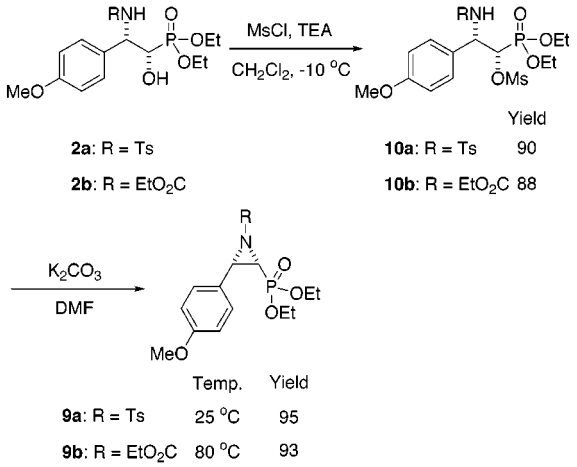
enic C-1 (δ = 31.1). This observation aided in assigning the C-1 protons (δ = 2.0, 2.1) by correlation with C-1 (δ = 31.1) using ^{1}H−^{13}C HETCOR. One of the C-1 protons (δ = 2.1) was then correlated with the C-2 proton (δ = 4.3) by ^{1}H−^{1}H COSY. The C-2 proton (δ = 4.3) was correlated with C-2 (δ = 69.2), and the C-3 proton (δ = 4.6) was correlated with C-3 (δ = 59.9) by ^{1}H−^{13}C HETCOR. The ^{13}C chemical shift for C-2 (δ = 69.2) was in better agreement with the expected chemical shift for carbon bound to a hydroxyl group (δ = 70.9, 77.6 reported for C-2, C-3 of the analogous diol)[15] than that of C-3 (δ = 59.9). Moreover, the ^{1}H−^{1}H COSY correlation found between the urethane proton (δ = 5.8) and the C-3 proton (δ = 4.6) confirmed the regiochemistry assignment.[16]

To assign the relative and absolute stereochemistry, as well as confirm the aforementioned regiochemistry argument, an X-ray crystal structure of a diastereomeric derivative of compound **5a** was sought. A suitable crystal of the (*S*)-*O*-methyl mandelate ester **8** (Scheme 1) was submitted for X-ray crystal determination. The X-ray structure (see the Supporting Information) confirmed the relative and absolute stereochemistry and regiochemistry hypothesized for **5a**. By analogy, the other phosphonates in Table 1 would be expected to have similar stereo and regiochemistries. Indeed, the ^{13}C NMR resonance for C-1 in the α-hydroxyphosphonate AA products (entries 1−6 of Table 1) was consistent in both the magnitude of the geminal coupling constant with phosphorus (J_1 = 159−163 Hz) and in chemical shift (δ 70.7−71.6). It is also worth noting that the sign of optical rotation for all the phosphonate AA products examined was consistent with the observed sign of optical rotation for AD-derived diols of the same unsaturated phosphonates (entries 1 and 2 in Table 1) and prepared using $(DHQ)_2PHAL$ ligand.[5a] These trends are consistent with the known regio- and stereochemistry for AA products of cinnamate substrates and with the stereochemistry of the asymmetric dihydroxylation (AD).[6]

Scheme 1



Scheme 2



To demonstrate their versatility, the phosphonate AA products **2a** and **2b** were converted into the corresponding *N*-tosyl or *N*-ethoxycarbonyl aziridines **9a** and **9b**, respectively (Scheme 2). A two-step process[17] involving initial mesylation of the hydroxyphosphonates followed by treatment of the isolated mesylates **10a** or **10b** with K_2CO_3 in DMF resulted in formation of the N-protected aziridine in high yield and high purity. Although heating above 80 °C was necessary for complete conversion of the *N*-ethoxycarbonyl-protected **10b**, no significant loss in yield or purity was observed. Neither step required more than a water workup for purification. It is noteworthy that the mesylates were considerably more crystalline than the starting hydroxyphosphonates. This fact could conceivably simplify the purification of the previous AA mixture, particularly in situations in which isolation of hydroxyphosphonates by recrystallization is not possible and the scale of the synthesis would make purification by chromatography undesirable.

(11) It is known that α-hydroxyphosphonates can undergo base-promoted cleavage giving aldehyde and dialkyl phosphite, and for 2,3-diol phosphonates isomerization of the resulting 2-hydroxyaldehyde to the hydroxymethyl ketone occurs [(a) Waszkuc, W.; Janecki, T.; Bodalski, R. *Synthesis* **1984**, 1025. (b) Kharasch, M. S.; Mosher, R. A.; Bengelsdorf, I. S. *J. Org. Chem.* **1960**, *25*, 1000]. Indeed, 2-hydroxyacetophenone was detected by GC in crude reaction mixtures for both **1a** and **1b**. Diethyl phosphite was also observed by ^{31}P NMR. Isolated product **1a** and the corresponding diol were both incubated separately with typical AA reaction media in order to better understand this side reaction. It was found that, under these conditions, **1a** showed very little change after 3 h, the time required for complete consumption of olefin (Table 1). However, after 30 h a peak at −2.5 ppm (56% of **1a**) in the ^{31}P NMR spectrum was evident. Although no diethyl phosphite was detected by NMR, it is reasonable that oxidation to the corresponding diethyl phosphate had occurred [diethyl phosphate has a reported chemical shift of +2.3 ppm in water: (c) Lerner, D. B.; Becktel, W. J.; Everett, R.; Goodman, M. *Biopolymers* **1984**, *23*, 2157]. In addition, a resonance at +10.0 ppm in the ^{1}H NMR indicated the presence of an aldehyde. Diol of entry 1 also showed some indication of cleavage under these conditions but to a lesser extent (a peak at −1.9 ppm in the ^{31}P NMR was only 14% of diol after 24 h). Only the cleavage products from the diol experiment included 2-hydroxyacetophenone (by GC). It is uncertain whether prolonged exposure of α-hydroxyphosphonate products to the AA reaction media is the only explanation for such byproducts, since a peak at −0.1 ppm (58% of **4a**) in the ^{31}P NMR was evident during formation of product **4a** after only 4 h reaction time.

(12) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; Chapter 7.

(13) O'Brien, P. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 326.

(14) Preliminary work using benzyl carbamate as the nitrogen source and the *p*-methoxystyrenyl phosphonate (entry 2, Table 1) indicated significantly poorer conversion than with ethyl carbamate (30−40% unreacted olefin). The reaction conditions are currently being optimized.

(15) (a) Yokomatsu, T.; Yamagishi, T.; Sada, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1998**, 781. (b) For ^{13}C NMR data of related α-amino and α-hydroxyphosphonates, see refs 4a and 5b, respectively.

(16) One of the reviewers pointed out that the assignment of the urethane proton could be confused with the hydroxyl proton, thus indicating the opposite regioisomer. This is unlikely for two reasons. First, the hydroxyl proton resonance in these sulfonamide and carbamate AA products is considerably broadened, and often difficult to distinguish from the baseline. Second, the urethane proton in **7b** (δ = 5.8−6.1 ppm dependent on concentration, d, J = 8.0 Hz) exhibits a similar chemical shift and coupling constant to that observed for the urethane proton in the mesylate **10b** (δ = 5.9 ppm, d, J = 8.0 Hz), in which no hydroxyl proton is present.

(17) Backvall, J.-E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 1953.

(18) The optical purity of **9a** was confirmed by comparison with *rac*-**9a** using chiral HPLC. The amount of minor enantiomer was below the limit of detection (see Supporting Information). Also, the ^{1}H and ^{31}P NMR spectra of **9a** gave no indication of diastereomers, which would have been generated had epimerization at C-1 or C-2 occurred during the two-step synthesis from **2a**. In order for racemization to have occurred, simultaneous loss of stereochemistry at both C-1 and C-2 would have had to take place.

The ability to readily generate *cis*-aziridines in high optical purity[18] by this methodology offers a valuable route toward these synthetically useful compounds.[19] Opening of such aziridines under a variety of conditions (e.g., nucleophilic/electrophilic addition) is currently being explored.

Experimental Section

General Methods. Unsaturated phosphonates were prepared by reaction of the appropriate aldehyde with the appropriate tetraalkyl methylenediphosphonate in CH_2Cl_2 by treatment with 50% NaOH solution and purified by Kuglerohr distillation under reduced pressure.[9a] Chloramine-T trihydrate and potassium osmate dihydrate were purchased from Acros and Colonial Metals, respectively. *tert*-Butyl hydroperoxide was prepared by a known procedure[20] and stored over $CaCl_2$ at 0 °C. CH_2Cl_2 was passed through basic alumina and stored over activated 3 Å molecular sieves before use in water-sensitive reactions. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively. ^{31}P NMR spectra were recorded at 162 MHz. ^{1}H−^{1}H COSY and ^{1}H−^{13}C HETCOR 2D NMR spectra were recorded on a 600 MHz spectrometer. ^{31}P NMR chemical shifts are relative to 85% H_3PO_4 (^{31}P NMR, $\delta_P = 0$ ppm, s) as an external reference. FT-IR spectra were recorded in the form of KBr disks or on NaCl plates. Enantiomeric excesses were determined by HPLC analysis using a Chiracel AD or OD-H column and varying concentrations of 2-propanol/hexanes as the mobile phase. Optical rotations were measured using 95% ethanol as solvent unless specified otherwise. Melting points are uncorrected. Unless specified, melting points and optical rotations for aminohydroxyphosphonate compounds were measured after recrystallization to the maximum enantiomeric purity as indicated by HPLC analysis. Elemental analyses were performed by Midwest Microlab (Indianopolis, IN). High-resolution mass spectrometry was performed by Dr. Gary Siuzdak (The Scripps Research Institute). X-ray crystal determination for compound **8** was performed by Dr. Michal Sabat (University of Virginia). Flash column chromatography was performed on Merck Kieselgel 60 (230−400 mesh). Analytical and preparative TLC were performed using precoated glass plates (Merck Kieselgel 60 F_{254}).

General Procedure for Aminohydroxylation Reactions of Unsaturated Phosphonates Using Chloramine-T Trihydrate. To a magnetically stirred solution of the unsaturated phosphonate (2.0 mmol), Chloramine-T trihydrate (1.69 g, 6.0 mmol), and $(DHQ)_2PHAL$ (80 mg, 0.10 mmol) in a mixture of CH_3CN (14 mL) and water (14 mL) was added $K_2OsO_2(OH)_4$ (30 mg, 0.08 mmol). As the osmate dissolved (5−10 min), the solution became an orange or pink color that changed to a deep green for all but the isopropyl-substituted phosphonate (Table 1, entry 4), which deepened to a red color. A change in color to a light yellow indicated the completion of the reaction (corresponding with disappearance of olefin as evidenced by TLC and/or ^{31}P NMR) with the exception of the β,γ-unsaturated phosphonate (Table 1, entry 7), which remained green even after 95% of the olefin had been consumed. The reaction was then quenched by addition of Na_2SO_3 (760 mg, 6.0 mmol) and allowed to stir for approximately 1 h. The phases were transferred to a separatory funnel with ethyl acetate (5 mL), and the bottom, aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. They were then concentrated under reduced pressure to yield a crude mixture of *p*-toluenesulfonamide and other byproducts including diol. Flash chromatography on silica gel (50 g) using a gradient of 50% hexanes/ethyl acetate (200 mL), followed by pure ethyl acetate (100 mL) to elute *p*-toluenesulfonamide, and then 10% methanol/ethyl acetate (150 mL) was utilized to elute the hydroxysulfonamide product in a minimum amount of solvent. Unless noted otherwise, purification of the desired product from contaminating side products was accomplished by recrystallization from 2-propanol (with a few drops of methanol added in cases where the solid was slow to dissolve with heating alone) at 0 °C.

(*S*)-(1*R,2*R**)-Diethyl [1-hydroxy-2-phenyl-2-(*p*-toluenesulfonamido)ethyl]phosphonate (1a)**: yield after recrystallization 180 mg (0.41 mmol, 21%) of a crystalline, white solid; mp 143−144 °C; $[\alpha]^{25}_D = +15.1$ (c =1.09) for sample of 91% ee; AD, 15% 2-propanol/hexane, 0.8 mL min^{-1} [17.3 min (*S*,*S*), 22.5 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, J = 7.5 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H), 2.27 (s, 3H), 3.90−4.00 (m, 3H), 4.12−4.22 (m, 2H), 4.72−4.76 (m, 1H), 5.06−5.09 (m, 1H), 6.69 (d, J = 7.5 Hz, 1H), 6.97−6.98 (m, 2H), 7.03−7.10 (m, 5H), 7.43−7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.08 (d, J = 5.5 Hz), 16.34 (d, J = 5.5 Hz), 21.27, 58.62 (d, J = 2.9 Hz), 62.63 (d, J = 6.9 Hz), 63.84 (d, J = 7.0 Hz), 71.52 (d, J = 160 Hz), 127.05, 127.30, 127.78, 128.83, 137.08 (d, J = 10.0 Hz), 137.76, 142.39; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.4; HRMS (FAB$^+$) calcd for $C_{19}H_{26}NO_6PSNa^+$ (M + Na$^+$) 450.1116, found 450.1107. Anal. Calcd for $C_{19}H_{26}NO_6PS$: C, 53.39; H, 6.13; N, 3.28. Found: C, 53.20; H, 6.04; N, 3.23.

(*S*)-(1*R,2*R**)-Diethyl [1-Hydroxy-2-(*p*-methoxyphenyl)-2-(*p*-toluenesulfonamido)ethyl]phosphonate (2a).** The reaction was scaled to 20 mmol of olefin: yield after recrystallization 2.8 g (6.1 mmol, 31%) of a fluffy, white solid; mp 152−153 °C; $[\alpha]^{25}_D = +13.8$ (c = 1.30) for sample of 99% ee; AD, 15% 2-propanol/hexane, 0.8 mL min^{-1} [28.2 min (*S*,*S*), 32.7 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 2.31 (s, 3H), 3.72 (s, 3H), 3.93−4.02 (m, 3H), 4.11−4.21 (m, 2H), 4.66−4.72 (m, 2H), 6.54 (d, J = 7.0 Hz, 1H), 6.60−6.62 (m, 2H), 7.02−7.05 (m, 4H), 7.45−7.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.10 (d, J = 5.8 Hz), 16.34 (d, J = 5.4 Hz), 21.27, 55.14, 58.18 (d, J = 3.1 Hz), 71.56 (d, J = 159 Hz), 113.18, 127.11, 128.80, 129.03, 129.16, 137.83, 142.28, 158.95; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.7; HRMS (FAB$^+$) calcd for $C_{20}H_{28}NO_7PSCs^+$ (M + Cs$^+$) 590.0378, found 590.0360. Anal. Calcd for $C_{20}H_{28}NO_7PS$: C, 52.51; H, 6.17; N, 3.06. Found: C, 52.47; H, 6.24; N, 3.05.

(*S*)-(1*R,2*R**)-Dimethyl [1-Hydroxy-2-(*p*-methoxyphenyl)-2-(*p*-toluenesulfonamido)ethyl]phosphonate (3a).** The reaction was performed on 2 mmol of olefin. Product was purified by flash chromatography using ethyl acetate/hexanes as in the general procedure to remove *p*-toluenesulfonamide, followed by a second flash column using 2% methanol in chloroform to remove most diol and regioisomer: yield 342 mg (0.69 mmol, 35%) of a viscous, clear oil including 13% impurities (by ^{31}P NMR); $[\alpha]^{25}_D = +11.0$ (c = 1.16) for sample of 88% ee; AD, 15% 2-propanol/hexane, 1.0 mL min^{-1} [22.4 min (*S*,*S*), 29.1 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.63 (d, J = 11.0 Hz, 3H), 3.70 (s, 3H), 3.76 (d, J = 10.5 Hz, 3H), 4.03−4.05 (m, 1H), 4.71−4.75 (m, 1H), 5.24 (br. s, 1H), 6.57−6.59 (m, 2H), 6.75 (d, J = 7.5 Hz, 1H), 6.98−7.02 (m, 4H), 7.43−7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.16, 53.14 (d, J = 5.8 Hz), 53.93, 55.03, 58.05 (d, J = 3.8 Hz), 71.45 (d, J = 160 Hz), 113.15, 126.98, 128.74, 128.85, 128.93 (d, J = 10.0 Hz), 137.69, 142.25, 158.84; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.0; HRMS (FAB$^+$) calcd for $C_{18}H_{24}NO_7PSNa^+$ (M + Na$^+$) 452.0909, found 452.0920. Anal. Calcd for $C_{18}H_{24}NO_7PS$: C, 50.35; H, 5.63; N, 3.26. Found: C, 50.34; H, 5.68; N, 3.22.

(*S*)-(1*R,2*R**)-Diisopropyl [1-Hydroxy-2-(*p*-methoxyphenyl)-2-(*p*-toluenesulfonamido)ethyl]phosphonate (4a).** After purification by preparative TLC, the product was recrystallized from 1:1 2-propanol/THF at 0 °C to obtain 205 mg (0.42 mmol, 21%) of a crystalline, white solid, mp 173−174 °C, which proved to be the racemate: AD, 10% 2-propanol/hexane, 1.0 mL min^{-1} [20.9 min (*R*,*R*), 26.5 min (*S*,*S*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, J = 6.5 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H), 2.31 (s, 3H), 3.72 (s, 3H), 3.86−3.94 (m, 1H), 4.55−4.60 (m, 1H), 4.60−4.66 (m, 1H), 4.68−4.75 (m, 1H), 4.90−4.92 (m, 1H), 6.47 (d, J = 6.5 Hz, 1H), 6.60−6.62 (m, 2H), 7.02−7.04 (m, 4H), 7.42−7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, for an unexplained reason dual peaks were observed; they are listed after their partner and starred) δ 21.15−21.29 (m), 22.98−24.60 (m), 55.06−55.17 (m), 58.14 (m), 71.42 (d, J = 161), 71.51* (d, J = 161), 71.69 (m), 72.49 (m),

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113.07, 113.19*, 126.95, 127.13*, 128.68, 128.82*, 129.04, 129.19*, 129.39, 129.46*, 137.91, 142.21, 158.95; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.2; HRMS (FAB$^+$) calcd for $C_{22}H_{32}NO_7PSNa^+$ (M + Na^+) 508.1535, found 508.1548. Anal. Calcd for $C_{22}H_{32}NO_7PS$: C, 54.42; H, 6.64; N, 2.88. Found: C, 54.38; H, 6.65; N, 2.90.

(*S*)-(1*R,2*R**)-Diethyl [1-hydroxy-2-(*p*-nitrophenyl)-2-(*p*-toluenesulfonamido)ethyl]phosphonate (5a):** yield after recrystallization; 376 mg (0.80 mmol, 40%) of a crystalline, white solid; mp 145−146 °C; $[\alpha]^{25}_D$ = + 27.1 (*c* =1.49) for sample of 99% ee; AD, 20% 2-propanol/hexane, 1.0 mL min^{-1} [18.1 min (*S*,*S*), 21.1 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.41 (t, *J* = 7.0 Hz, 3H), 2.27 (s, 3H), 4.02−4.10 (m, 3H), 4.31−4.37 (m, 2H), 4.91−4.94 (m, 1H), 5.70 (m, 1H), 6.97−6.99 (m, 2H), 7.25−7.30 (m, 3H), 7.46−7.48 (m, 2H), 7.89−7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.14 (d, *J* = 5.6 Hz), 16.42 (d, *J* = 5.1 Hz), 21.20, 58.30, 62.83 (d, *J* = 7.1 Hz), 64.53 (d, *J* = 7.4 Hz), 71.27 (d, *J* = 160 Hz), 122.77, 127.05, 128.85, 128.98, 137.47, 143.23, 144.45 (d, *J* = 11.0 Hz), 146.93; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.4; HRMS (FAB$^+$) calcd for $C_{19}H_{25}N_2O_8PSNa^+$ (M + Na^+) 495.0967, found 495.0954. Anal. Calcd for $C_{19}H_{25}N_2O_8PS$: C, 48.30; H, 5.33; N, 5.93. Found: C, 48.22; H, 5.26; N, 5.89.

(*S*)-(1*R,2*R**)-Diethyl [1-hydroxy-2-(2-naphthyl)-2-(*p*-toluenesulfonamido)ethyl]phosphonate (6a):** yield after recrystallization 286 mg (0.60 mmol, 30%) of a white powder; mp 151−152 °C; $[\alpha]^{25}_D$ = +28.5 (*c* =1.05) for sample of 93% ee; AD, 10% 2-propanol/hexane, 1.0 mL min^{-1} [33.0 min (*S*,*S*), 36.9 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.5 Hz, 3H), 2.06 (s, 3H), 3.95−4.00 (m, 2H), 4.11−4.15 (m, 1H), 4.17−4.25 (m, 2H), 4.62 (br s, 1H), 4.93−4.97 (m, 1H), 6.70 (br s, 1H), 6.77−6.79 (m, 2H), 7.25−7.26 (m, 1H), 7.40−7.42 (m, 4H), 7.51 (s, 1H), 7.54−7.56 (m, 1H), 7.59−7.61 (m, 1H), 7.70−7.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.01 (d, *J* = 5.5 Hz), 16.33 (d, *J* = 5.1 Hz), 20.92, 58.84 (d, *J* = 2.8 Hz), 62.64 (d, *J* = 7.0 Hz), 63.90 (d, *J* = 7.0 Hz), 71.51 (d, *J* = 159 Hz), 125.43, 125.61, 125.68, 126.91, 127.18, 127.26, 127.47, 127.75, 128.55, 132.59, 132.61, 134.11 (d, *J* = 10.0 Hz), 137.63, 142.36; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.8; HRMS (FAB$^+$) calcd for $C_{23}H_{28}NO_6PSNa^+$ (M + Na^+) 500.1273, found 500.1285. Anal. Calcd for $C_{23}H_{28}NO_6PS$: C, 57.85; H, 5.91; N, 2.93. Found: C, 57.17; H, 5.76; N, 2.96.

(*R*)-(2*R,3*S**)-Diethyl [2-hydroxy-3-phenyl-3-(*p*-toluenesulfonamido)propyl]phosphonate (7a):** yield after recrystallization 180 mg (0.41 mmol, 20%) of a fluffy, white solid; mp 155−156 °C; $[\alpha]^{25}_D$ = +7.2 (*c* =0.58) for sample of 94% ee; AD, 15% 2-propanol/hexane, 0.8 mL min^{-1} [24.3 min (*R*,*S*), 27.1 min (*S*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.82 (m, 1H), 2.06 (td, *J* = 15.5, 10.0 Hz, 1H), 2.32 (s, 3H), 4.03−4.21 (m, 6H), 4.22 (m, 1H), 5.85 (br. s, 1H), 7.05−7.07 (m, 4H), 7.13−7.15 (m, 3H), 7.45−7.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.24 (d, *J* = 5.1 Hz), 21.30, 30.42 (d, *J* = 141 Hz), 61.94 (d, *J* = 6.4 Hz), 62.29 (d, *J* = 6.3 Hz), 63.26 (d, *J* = 20 Hz), 69.69 (d, *J* = 4 Hz), 126.89, 127.35, 127.47, 128.16, 129.00, 137.59, 138.06, 142.60; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.5; HRMS (FAB$^+$) calcd for $C_{20}H_{28}NO_6PSNa^+$ (M + Na^+) 464.1273, found 464.1264. Anal. Calcd for $C_{20}H_{28}NO_6PS$: C, 54.41; H, 6.39; N, 3.17. Found: C, 54.64; H, 6.44; N, 3.08.

General Procedure for Aminohydroxylation Reactions of Unsaturated Phosphonates Using Ethyl *N*-Chloro-*N*-sodiocarbamate. To a magnetically stirred solution of NaOH (1.0 M, 6.0 mL, 6.0 mmol) was added urethane (570 mg, 6.4 mmol). After the urethane had dissolved (1−2 min), *tert*-butyl hypochlorite (660 mg, 6.0 mmol) was dispensed in a dropwise fashion. The solution was subsequently diluted with water (8 mL) and *n*-propanol (14 mL). $(DHQ)_2PHAL$ (80 mg, 0.10 mmol) and unsaturated phosphonate (2.0 mmol) were then added. After complete dissolution of ligand and olefin, $K_2OsO_2(OH)_4$ (30 mg, 0.08 mmol) was added to the solution. The color varied somewhat with substrate (and was not always reproducible with the same substrate), but generally a pink or orange color persisted through the entire reaction. A pale yellow or green would occasionally correspond with a complete reaction, but the color difference was found not to be a reliable indicator of conversion as with the sulfonamides. For phosphonate **1b**, 17% unreacted olefin (relative to all other ^{31}P NMR signals) was still present after 18 h. Further reaction time did not improve conversion significantly. The reactions were monitored, quenched, and subjected to a workup similar to that of the hydroxysulfonamides. Noncrystalline carbamates were generated on a 0.5 mmol scale and purified by preparative TLC (5% MeOH/$CHCl_3$; **1b**, **4b**, **5b**, **7b**). Unless specified otherwise, crystallization of solid hydroxycarbamate compounds was performed from diethyl ether at −30 °C (**2b**, **6b**). Seeding with a small amount of solid product, which had been purified by preparative TLC, was typically required to induce crystallization.

(*S*)-(1*R,2*R**)-Diethyl [1-hydroxy-2-phenyl-2-(*O*-ethylcarbamyl)ethyl]phosphonate (1b):** yield after preparative TLC 61 mg (0.16 mmol, 32%) of a viscous, yellow oil including 10% impurities (by ^{31}P NMR); $[\alpha]^{25}_D$ = + 18.0 (*c* =1.57) for sample in 93% ee; AD, 20% 2-propanol/hexane, 1.0 mL min^{-1} [5.03 min (*S*,*S*), 6.33 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (m, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 3.91−4.22 (m, 7H), 5.13 (br. s, 1H), 5.38 (br. s, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 7.22−7.26 (m, 1H), 7.29−7.32 (m, 2H), 7.32−7.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.50, 16.24 (d, *J* = 5.6 Hz), 16.34 (d, *J* = 5.5 Hz), 55.04, 60.77, 62.78 (d, *J* = 6.9 Hz), 63.38 (d, *J* = 7.0 Hz), 71.18 (d, *J* = 160 Hz), 126.80, 127.32, 128.23, 140.25 (d, *J* = 13.5 Hz), 156.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.2; IR (KBr) ν 1721 (C═O, urethane) cm^{-1}; HRMS (FAB$^+$) calcd for $C_{15}H_{24}NO_6PNa^+$ (M + Na^+) 368.1239, found 368.1231. Anal. Calcd for $C_{15}H_{24}NO_6P$: C, 52.17; H, 7.00; N, 4.06. Found: C, 52.10; H, 7.05; N, 4.02.

(*S*)-(1*R,2*R**)-Diethyl [1-hydroxy-2-(*p*-methoxyphenyl)-2-(*O*-ethylcarbamyl)ethyl]phosphonate (2b):** yield after recrystallization 336 mg (0.90 mmol, 45%) of a fluffy, white solid; mp 86−87 °C; $[\alpha]^{25}_D$ = + 30.2 (*c* =1.50) for sample of 99% ee; AD, 15% 2-propanol/hexane, 0.5 mL min^{-1} [15.7 min (*S*,*S*), 26.3 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (m, 3H), 1.26 (t, *J* = 7.0 Hz), 1.34 (t, *J* = 7.0 Hz, 3H), 3.79 (s, 3H), 4.05−4.15 (m, 5H), 4.18−4.23 (m, 2H), 4.40−4.70 (m, 1H), 5.08 (br. s, 1H), 6.40 (m, 1H), 6.85−6.87 (m, 2H), 7.30−7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.52, 16.28 (d, *J* = 5.0 Hz), 16.37 (d, *J* = 5.0 Hz), 54.57, 55.19, 60.75, 62.77 (d, *J* = 6.3 Hz), 63.36 (d, *J* = 7.5 Hz), 71.33 (d, *J* = 160 Hz), 113.75, 128.02, 132.41 (d, *J* = 14.0 Hz), 156.20, 158.80; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.0; IR (KBr) ν 1706 (C═O, urethane) cm^{-1}; HRMS (FAB$^+$) calcd for $C_{16}H_{26}NO_7PCs^+$ (M + Cs^+) 508.0501, found 508.0511. Anal. Calcd for $C_{16}H_{26}NO_7P$: C, 51.19; H, 6.98; N, 3.73. Found: C, 50.97; H, 7.02; N, 3.78.

(*S*)-(1*R,2*R**)-Dimethyl [1-Hydroxy-2-(*p*-methoxyphenyl)-2-(*O*-ethylcarbamyl)ethyl]phosphonate (3b).** The reaction was performed on 1 mmol olefin. After the general isolation procedure, product was recrystallized from 2-propanol to obtain 110 mg (0.32 mmol, 32%) of a fluffy, white solid: mp 111−112 °C; $[\alpha]^{25}_D$ = +33.0 (*c* =1.80) for sample of 99% ee; AD, 10% 2-propanol/hexane, 1.0 mL min^{-1} [14.3 min (*S*,*S*), 23.0 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14−1.17 (m, 3H), 3.67 (d, *J* = 10.0 Hz, 3H), 3.75 (s, 3H), 3.79 (d, *J* = 10.5 Hz, 3H), 4.04 (q, *J* = 7.0 Hz, 2H), 4.14 (br. s, 1H), 5.06 (br. s, 1H), 5.38 (br. s, 1H), 6.59 (d, *J* = 9 Hz, 1H), 6.82−6.84 (m, 2H), 7.27−7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.42, 53.16 (d, *J* = 6.8 Hz), 53.73 (d, *J* = 3.0 Hz), 54.52, 55.12, 60.82, 71.10 (d, *J* = 160 Hz), 113.63, 127.95, 132.05 (d, *J* = 13.5 Hz), 156.22, 158.83; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.1; IR (KBr) ν 1706 (C═O, urethane) cm^{-1}; HRMS (FAB$^+$) calcd for $C_{14}H_{22}NO_7PNa^+$ (M + Na^+) 370.1032, found 370.1038. Anal. Calcd for $C_{14}H_{22}NO_7P$: C, 48.42; H, 6.38; N, 4.03. Found: C, 48.76; H, 6.55; N, 4.01.

(*S*)-(1*R,2*R**)-Diisopropyl [1-Hydroxy-2-(*p*-methoxyphenyl)-2-(*O*-ethylcarbamyl)ethyl]phosphonate (4b).** After purification by preparative TLC, the product crystallized from ether at room temperature to obtain 70 mg (0.17 mmol, 35%) of a fluffy, white solid: mp 44−45 °C; $[\alpha]^{25}_D$ = +26.2 (*c* =1.20) for sample of 99% ee; AD, 5% 2-propanol/hexane, 1.0 mL min^{-1} [18.5 min (*S*,*S*), 32.7 min (*R*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17−1.21 (m, 6H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.34−1.36 (m, 6H), 3.76 (s, 3H), 3.98−4.05 (m, 3H), 4.60−4.61 (m, 1H), 4.78−4.84 (m, 1H), 5.07 (br. s, 1H), 5.54 (br. s, 1H), 6.70 (m, 1H), 6.82−6.83 (m, 2H), 7.28−7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.52, 23.62, 23.66, 23.94, 24.08, 54.63, 55.10, 60.49, 71.56 (d, *J* = 163 Hz), 71.62 (d, *J* = 7.4 Hz), 72.11 (d, *J* = 7.4 Hz), 113.52, 127.91, 132.80 (d, *J* = 13.0 Hz), 156.00, 158.72; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.3; IR (KBr) ν 1725 (C═O, urethane) cm^{-1}; HRMS (FAB$^+$) calcd for $C_{18}H_{30}NO_7PNa^+$ (M + Na^+) 426.1658, found

426.1668. Anal. Calcd for $C_{18}H_{30}NO_7P$: C, 53.59; H, 7.50; N, 3.47. Found: C, 53.29; H, 7.41; N, 3.39.

(*S*)-(1*R,2*R**)-Diethyl [1-hydroxy-2-(*p*-nitrophenyl)-2-(*O*-ethylcarbamyl)ethyl]phosphonate (5b):** yield after preparative TLC 109 mg (0.27 mmol, 53%) of a viscous, orange oil including less than 5% impurities by ^{31}P NMR; $[\alpha]^{25}_D = +23.2$ ($c = 3.61$) for sample of 97% ee; AD, 10% 2-propanol/hexane, 0.8 mL min^{-1} [16.3 min (*S*,*S*), 31.2 min (*R*,*R*)]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (m, 3H), 1.28 (t, $J = 7.0$ Hz, 3H), 1.39 (t, $J = 7.0$ Hz, 3H), 4.07−4.12 (m, 5H), 4.25−4.29 (m, 2H), 5.22 (br. s, 1H), 5.54 (br. s, 1H), 6.89 (br. s, 1H), 7.56−7.58 (m, 2H), 8.19−8.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.52, 16.30 (d, $J = 6.0$ Hz), 16.40 (d, $J = 5.4$ Hz), 55.13, 61.15, 63.21 (d, $J = 7.9$ Hz), 63.87 (d, 7.6 Hz), 70.72 (d, $J = 161$ Hz), 123.53, 127.91, 147.29, 147.85 (d, $J = 13.3$ Hz), 156.11; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.2; IR (NaCl plates) ν 1717 (C=O, urethane) cm^{-1}; HRMS (FAB^+) calcd for $C_{15}H_{23}N_2O_8PNa^+$ ($M + Na^+$) 413.1090, found 413.1079. Anal. Calcd for $C_{15}H_{23}N_2O_8P$: C, 46.16; H, 5.94; N, 7.18. Found: C, 45.78; H, 6.05; N, 7.07.

(*S*)-(1*R,2*R**)-Diethyl [1-hydroxy-2-(*β*-naphthyl)-2-(*O*-ethylcarbamyl)ethyl]phosphonate (6b)**: yield after recrystallization 420 mg (1.06 mmol, 53%) of a slightly yellow, crystalline solid; mp 112−113 °C; $[\alpha]^{25}_D = +43.3$ ($c = 1.37$) for sample of 99% ee; AD, 10% 2-propanol/hexane, 0.8 mL min^{-1} [23.4 min (*S*,*S*), 32.5 min (*R*,*R*)]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19−1.22 (m, 6H), 1.35 (t, $J = 7.0$ Hz, 3H), 4.05−4.12 (m, 4H), 4.20−4.27 (m, 3H), 4.92 (br. s, 1H), 5.31 (br. s, 1H), 6.63 (br. s, 1H), 7.44−7.51 (m, 3H), 7.80−7.83 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.42, 16.09 (d, $J = 4.3$ Hz), 16.28 (d, $J = 5.2$ Hz), 55.12, 60.69, 62.70 (d, $J = 6.6$ Hz), 63.37 (d, $J = 6.9$), 71.02 (d, $J = 160$ Hz), 124.92, 125.59, 125.82, 127.37, 127.79, 127.85, 132.66, 133.06, 137.76 (d, $J = 12.0$ Hz), 156.12; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.9; IR (KBr) ν 1731 (C=O, urethane) cm^{-1}; HRMS (FAB^+) calcd for $C_{19}H_{26}NO_6PNa^+$ ($M + Na^+$) 418.1395, found 418.1385. Anal. Calcd for $C_{19}H_{26}NO_6P$: C, 57.72; H, 6.63; N, 3.54. Found: C, 57.66; H, 6.63; N, 3.49.

(*R*)-(2*R,3*S**)-Diethyl [2-Hydroxy-3-phenyl-3-(*O*-ethylcarbamyl)propyl]phosphonate (7b).** The reaction was performed on 1 mmol of olefin. After the general isolation procedure, the racemate crystallized from 2-propanol at 0 °C. The mother liquor was then purified by preparative TLC, and 103 mg (0.29 mmol, 29%) of a viscous, yellow oil was obtained: $[\alpha]^{25}_D = +15.7$ ($c = 4.56$) for sample of 90% ee; AD, 10% 2-propanol/hexane, 1.0 mL min^{-1} [9.73 min (*R*,*S*), 15.3 min (*S*,*R*)]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19−1.25 (m, 3H), 1.30 (t, $J = 7.0$ Hz, 3H), 1.32 (t, $J = 7.0$ Hz, 3H), 1.93−2.04 (m, 1H), 2.12 (td, $J = 15.5$ Hz, 10.5 Hz, 1H), 4.04−4.13 (m, 6H), 4.28 (m, 2H), 4.64 (br. s, 1H), 6.10 (d, 1H, $J = 8.0$ Hz), 7.25−7.28 (m, 1H), 7.32−7.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.45, 16.27 (d, $J = 6.0$ Hz), 31.08 (d, 139 Hz), 59.87 (d, $J = 18.4$ Hz), 60.89, 61.88 (d, $J = 6.4$ Hz), 62.14 (d, $J = 4.3$ Hz), 69.24 (d, $J = 4.5$ Hz), 126.79, 127.44, 128.41, 140.36, 156.58; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.9; IR (NaCl plates) ν 1715 (C=O, urethane) cm^{-1}; HRMS (FAB^+) calcd for $C_{16}H_{26}NO_6PCs^+$ ($M + Cs^+$) 492.0552, found 492.0563. Anal. Calcd for $C_{16}H_{26}NO_6P$: C, 53.48; H, 7.29; N, 3.90. Found: C, 53.57; H, 7.35; N, 3.86.

(*S*)-(1*R,2*R**)-Diethyl [1-(*S*-α-Methoxyphenylacetyloxy)-2-(*p*-nitrophenyl)-2-(*p*-toluenesulfonamido)ethyl]phosphonate (8).** To a magnetically stirred solution of **5a** (780 mg, 1.65 mmol; 99% ee) in CH_2Cl_2 (2 mL) was added (*S*)-(+)-α-methoxyphenylacetic acid (274 mg, 1.65 mmol) followed by DMAP (5 mg, 0.04 mmol) and then DCC (374 mg, 1.82 mmol) at 0 °C. The reaction was allowed to warm to room temperature over 30 min. The white precipitate, dicyclohexylurea, was removed by filtration, and the filtrate was concentrated under reduced pressure. Recrystallization of crude **8** from 1:1 toluene/hexanes yielded 908 mg (1.47 mmol, 89%) of a white powder. To obtain X-ray quality crystals, **8** was dissolved in chloroform (5 mL) in an open scintillation vial that was placed inside a larger glass container containing *n*-pentane. Slow diffusion of *n*-pentane into the chloroform solution over a period of 5 days resulted in suitable crystals for X-ray diffraction. A mixture of diastereomers of **8** was similarly prepared (excluding the second recrystallization by slow diffusion) from *rac*-**5a** in order to confirm the diastereomeric purity of **8**. The de for the enriched diastereomer after recrystallization by slow diffusion was only 96% (compared with 99% ee for the starting material **5a**) by ^{31}P NMR. The ee of (*S*)-(+)-α-methoxyphenylacetic acid was not checked. Surprisingly, it was found that the mp for the mixture of diastereomers (125−133 °C) was higher than the mp of the enriched diastereomer (119−121 °C): $[\alpha]^{25}_D = +16.5$ ($c = 1.62$) for sample of 96% de; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, $J = 7.2$ Hz, 3H), 1.21 (t, $J = 7.0$ Hz, 3H), 2.35 (s, 3H), 3.33 (s, 3H), 3.85−3.96 (m, 2H), 3.97−4.10 (m, 2H), 4.74 (s, 1H), 4.78−4.82 (m, 1H), 5.31 (dd, 1H, $J = 3.5$, 10.8 Hz, 1H), 6.16 (d, $J = 6.2$ Hz, 1H), 6.81−6.82 (m, 2H), 7.13−7.15 (m, 2H), 7.34−7.36 (m, 2H), 7.42−7.51 (m, 3H), 7.52−7.54 (m, 2H), 7.66−7.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.08 (d, $J = 6.0$ Hz), 16.15 (d, $J = 6.0$ Hz), 21.34, 56.14, 57.17, 63.37 (d, $J = 6.5$ Hz), 63.74 (d, $J = 7.2$ Hz), 68.99 (d, $J = 166$ Hz), 81.88, 122.90, 127.13, 127.47, 127.97, 128.93, 129.31, 129.46, 135.09, 136.76, 143.38 (d, $J = 9.8$ Hz), 143.67, 146.96, 168.20 (d, $J = 4.6$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.1 (major diastereomer, 98%), 15.5 (minor diastereomer, 2%); IR (KBr) ν 1764 (C=O, ester) cm^{-1}; HRMS (MALDI-FTMS) calcd for $C_{28}H_{33}N_2O_{10}PSNa^+$ ($M + Na^+$) 643.1491, found 643.1569. Anal. Calcd for $C_{28}H_{33}N_2O_{10}PS$: C, 54.19; H, 5.36; N, 4.51. Found: C, 54.21; H, 5.37; N, 4.48.

(*S*)-(1*R,2*R**)-Diethyl [1-Methanesulfonyloxy-2-(*p*-methoxyphenyl)-2-(*p*-toluenesulfonamido)ethyl]phosphonate (10a).** To a magnetically stirred solution of hydroxysulfonamide **2a** (1.03 g, 2.25 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.94 mL, 6.8 mmol) followed by methanesulfonyl chloride (0.35 mL, 4.5 mmol) at −10 °C. The reaction was quenched after 15 min by the addition of water (10 mL). The mixture was transferred to a separatory funnel with CH_2Cl_2 (5 mL), and the top, aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic phases were washed with a 10% solution of $NaHCO_3$ (10 mL) and brine (10 mL) and then dried over $MgSO_4$. Concentration under reduced pressure yielded 1.26 g of an impure, yellow solid. Although formation of aziridine **9a** in the next step of the sequence (Scheme 2) was apparently not retarded by such impurities in the mesylate **10a**, purification was possible by recrystallization from 30% methanol/2-propanol at room temperature to give 1.08 g (2.02 mmol, 90%) of a crystalline, white solid: mp 158−159 °C; $[\alpha]^{25}_D = +21.8$ ($c = 1.10$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (q, $J = 6.6$ Hz, 6H), 2.33 (s, 3H), 3.02 (s, 3H), 3.73 (s, 3H), 3.92−4.08 (m, 4H), 4.87−4.94 (m, 2H), 5.85−5.86 (m, 1H), 6.67−6.69 (m, 2H), 7.05−7.10 (m, 4H), 7.50−7.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9−16.4 (m), 21.1−21.5 (m), 39.12−39.28 (m), 55.17 (d, $J = 15.0$ Hz), 57.20 (d, $J = 5.0$ Hz), 63.1−63.2 (m), 63.9−64.1 (m), 77.09 (d, $J = 165$ Hz), 113.54 (d, $J = 16.3$ Hz), 127.15 (d, $J = 26.3$ Hz), 127.44 (d, $J = 6.0$ Hz), 128.9−129.2 (m), 137.35, 143.00, 159.48; ^{31}P NMR (162 MHz, $CDCl_3$) δ 15.5; HRMS (FAB^+) calcd for $C_{21}H_{30}NO_9PS_2Cs^+$ ($M + Cs^+$) 668.0154, found 668.0169. Anal. Calcd for $C_{21}H_{30}NO_9PS_2$: C, 47.10; H, 5.65; N, 2.62. Found: C, 47.21; H, 5.73; N, 2.59.

(*S*)-(1*R,2*R**)-Diethyl [1-Methanesulfonyloxy-2-(*p*-methoxyphenyl)-2-(*O*-ethylcarbamyl)ethyl]phosphonate (10b).** Mesylate **10b** was prepared and purified in the same manner as the sulfonamide **10a** above, except the reaction was scaled to 5.00 mmol of **2b** and the recrystallization solvent was pure 2-propanol, to give 2.0 g (4.4 mmol, 88%) of a white powder: mp 115−116 °C; $[\alpha]^{25}_D = +32.1$ ($c = 1.38$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.22−1.24 (m, 6H), 1.32−1.35 (m, 3H), 2.89 (s, 3H), 3.79 (s, 3H), 4.10−4.19 (m, 6H), 5.05 (dd, $J = 10.0$, 5.0 Hz, 1H), 5.30−5.32 (m, 1H), 5.87 (d, $J = 8.0$ Hz, 1H), 6.88−6.90 (m, 2H), 7.28−7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.37, 16.12 (m), 38.89, 53.90, 55.11, 61.03, 63.37 (m), 78.17 (d, $J = 164$ Hz), 113.86, 128.12, 129.55 (d, $J = 6.8$ Hz), 155.46, 159.36; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.1; IR (KBr): ν 1727 (C=O, urethane) cm^{-1}; HRMS (FAB^+) calcd for $C_{17}H_{28}NO_9PSNa^+$ ($M + Na^+$) 476.1120, found 476.1128. Anal. Calcd for $C_{17}H_{28}NO_9PS$: C, 45.03; H, 6.22; N, 3.09. Found: C, 44.83; H, 6.16; N, 3.01.

(*R*)-(1*R,2*S**)-Diethyl [2-(*p*-Methoxyphenyl)-1,2-[*N*-(*p*-toluenesulfonyl)aziridino]ethyl]phosphonate (9a).** To a magnetically stirred solution of mesylate **10a** (0.920 g, 1.72 mmol) in DMF (10 mL) was added K_2CO_3 (1.2 g, 8.6 mmol). The suspension was stirred at room temperature for 2 h. At this point, the viscous mixture was transferred to a separatory funnel with CH_2Cl_2 (20 mL) and washed with water (5 × 20 mL) and brine (20 mL). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure to yield 720 mg (1.64 mmol, 95%) of a viscous, yellow oil that was pure by NMR: $[\alpha]^{25}_D$

= +63.5 (c =3.66) for sample of 99% ee; OD-H, 20% 2-propanol/hexane, 0.5 mL min^{-1} [16.3 min (*R*,*S*), 17.5 min (*S*,*R*)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, J = 7.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H), 2.43 (s, 3H), 3.06 (dd, J = 14.5, 7.5 Hz, 1H), 3.51−3.59 (m, 1H), 3.74 (s, 3H), 3.77−3.99 (m, 3H), 4.01 (t, J = 8.5 Hz, 1H), 6.77−6.80 (m, 2H), 7.23−7.34 (m, 2H), 7.34−7.35 (m, 2H), 7.87−7.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.06, 21.60, 38.68 (d, J = 205 Hz), 43.78 (d, J = 4.6 Hz), 55.14, 62.48 (m), 113.39, 123.68, 128.30, 128.89, 129.76, 133.83, 145.12, 159.49; ^{31}P NMR (162 MHz, $CDCl_3$) δ 15.7; HRMS (FAB$^+$) calcd for $C_{20}H_{27}NO_6PS^+$ (M + H$^+$) 440.1297, found 440.1285. Anal. Calcd for $C_{20}H_{26}NO_6PS$: C, 54.66; H, 5.96; N, 3.19. Found: C, 54.40; H, 5.98; N, 3.27.

(*R*)-(1*R,2*S**)-Diethyl [1,2-[*N*-(Ethoxycarbonyl)aziridino]-2-(*p*-methoxyphenyl)ethyl]phosphonate (9b).** Aziridine **9b** was prepared by the same method as **9a** above, except the reaction was scaled to 4.00 mmol of **10b** and it required heating at 80 °C for 3 h. The product was isolated as 1.33 g (3.72 mmol, 93%) of a viscous, yellow oil and was pure by NMR: $[\alpha]^{25}_D$ = +24.3 (c =1.56); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 2.87 (dd, J = 17.0, 7.0 Hz, 1H), 3.67−3.76 (m, 1H), 3.80 (s, 3H), 3.83 (t, J = 7.0 Hz, 1H), 3.87−4.06 (m, 3H), 4.20−4.26 (m, 2H), 6.87−6.89 (m, 2H), 7.41−7.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.25, 16.20 (m), 37.93 (d, J = 206 Hz), 43.10 (d, J = 4.9 Hz), 55.25, 62.27 (d, J = 6.1 Hz), 62.41 (d, J = 6.4 Hz), 63.27, 113.41, 125.54, 128.98, 159.44, 162.54 (d, J = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.0; IR (NaCl plates) ν 1729 (C=O, urethane) cm^{-1}; HRMS (FAB$^+$) calcd for $C_{16}H_{24}NO_6PNa^+$ (M + Na$^+$) 380.1239, found 380.1229. Anal. Calcd for $C_{16}H_{24}NO_6P$: C, 53.78; H, 6.77; N, 3.92. Found: C, 53.55; H, 6.77; N, 3.89.

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Supporting Information Available: ^{1}H NMR spectra for compounds **2b** and **5a**; ^{1}H, ^{13}C, ^{1}H−^{1}H COSY, and ^{1}H−^{13}C HETCOR 2D NMR spectra with partial assignments for **7b**; the ORTEP structure and ^{31}P NMR spectrum for **8**; ^{1}H and ^{31}P NMR spectra for **9a** as well as chiral HPLC traces for **9a** and *rac*-**9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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