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Sulfinimine-Mediated Asymmetric Synthesis of β-Hydroxy α-Amino Phosphonates

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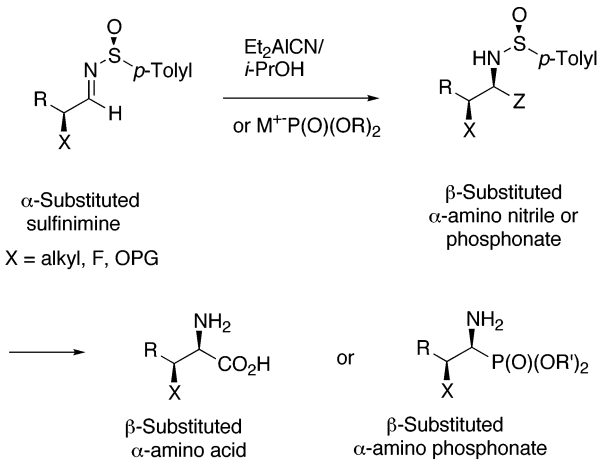
The addition of potassium dialkyl phosphites to enantiopure O-protected α-hydroxy sulfinimine pseudoenantiomers affords β-hydroxy α-amino phosphonates in good yield and de. The reaction exhibits a strong match−mismatch effect.

Although the phosphonic and carboxylic acid groups differ considerably with respect to shape, size, and acidity, α-amino phosphonic acids have found extensive use as surrogates and structural analogues of α-amino acids.[1,2] For these reasons, and the fact that chirality is an important issue for biologically active molecules, the asymmetric synthesis of α-amino phosphonic acids and their functionalized derivatives is an important objective. Recent efforts in our group and other groups have focused on the asymmetric syntheses of α-amino acids and α-amino phosphonic acids, including functionalized examples, using sulfinimines (*N*-sulfinylimines).[3,4] Such studies may also provide critical information on the chemical reactivity/selectivity of the phosphonate group as compared to carboxylate esters. This information is of fundamental importance to the understanding of the role of the phosphonate group in biorelevant transformations. The overall strategy in our investigations entails the addition of cyanide (ethylaluminum cyanoisopropoxide) or a metal phosphonate to an α-substituted sulfinimine (Scheme 1). We describe here a useful method for the enantioselective synthesis of β-hydroxy α-amino phosphonates from O-protected α-hydroxy sulfinimines.

SCHEME 1



β-Hydroxy α-amino phosphonates can be envisioned as analogues of β-hydroxy α-amino acids. These later amino acids are found in nature (threonine, serine, and β-hydroxy proline), as constituents of more complex natural products, and as chiral building blocks.[5] The asymmetric synthesis of β-hydroxy α-amino phosphonates has been the subject of only a few studies.[1b] For example, aldehydes reportedly react with (isocyanomethyl)phosphonates in the presence of a chiral gold catalyst to give oxazoline phosphonates that can be hydrolyzed to β-hydroxy α-amino phosphonates in high ee and good yield.[6] In addition, Noyori and co-workers employed the BINAP−Ru-catalyzed hydrogenation of α-amido β-keto phosphonic esters to prepare these materials with excellent enantio- and diastereoselective control.[7] Another route to β-hydroxy α-amino phosphonates involves the addition of trimethylsilyldiethyl phosphite to enantiopure bis-silylated α-hydroxy aldimines.[8] Other less general methods include the alcoholysis of aziridine phospho-

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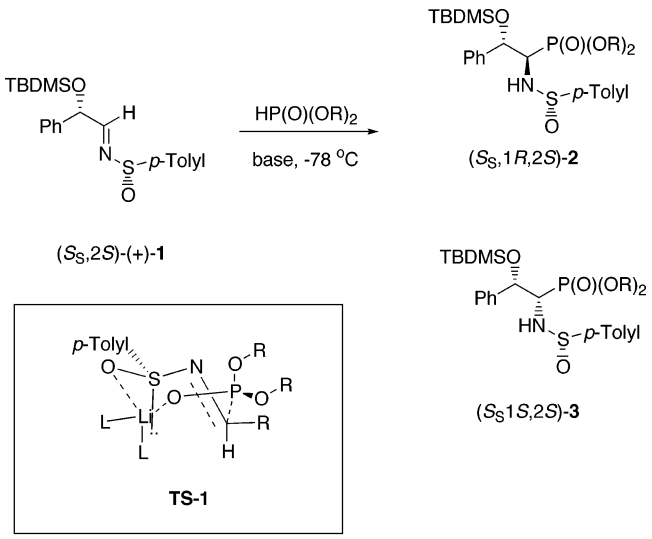
SCHEME 2



nates,[9] the reaction of *N*,*O*-acetals with phosphates,[10a] and the addition of phosphite to chiral *N*-benzyl nitrones.[10b]

Results and Discussion

Initially, we explored the reaction of metal phosphites to the known α-hydroxy sulfinimine (S_S,2*S*)-(+)-**1**, which was obtained from (1*S*)-(+)-mandelic acid and commercially available (*S*)-(−)-*p*-toluenesulfinamide.[3e] Addition of lithium diethyl phosphite proceeded very cleanly, affording the corresponding *N*-sulfinylamino phosphonates **2** and **3** in a 77:23 ratio of a nonseparable mixture of diastereomers (Scheme 2, Table 1, entry 1). The absolute stereochemistry of the product of the addition of organometallic reagents (CN, enolates, Grignard reagents) to sulfinimines is controlled by the *N*-sulfinyl group and predicted by a six-membered chelated chairlike transition state.[11] For metal phosphite additions to sulfinimines, a seven-membered twisted chairlike transitions state, **TS-1**, where the metal cation is chelated to both the sulfinyl and phosphite oxygens, has been evoked to explain the stereochemistry.[4c] Consequently, the erythro product (S_S,1*R*,2*S*)-**2** is predicted to be the dominant isomer for the additions outlined in Scheme 2, and the prediction was confirmed as discussed below.

The addition of dimethyl and diisopropyl phosphites resulted in similar diastereomeric excess, which indicates the size of the nucleophilic phosphite has no effect on the selectivity.[12] The effect of the counterion and the solvent on the diastereoselectivity were examined next. The use of NaHMDS as a base deteriorated the selectivity (Table 1, entry 4), while an improvement (93:7) was observed when KHMDS was employed (Table 1, entry 5). Of the various solvents screened, THF was found to be the solvent of choice to obtain enhanced diastereoselectivity.

To examine the possibility of a match−mismatch effect (double diastereodifferentiation) on the selectivity, all four possible isomers of the sulfinimines derived from (*S*)-(+)- and (*R*)-(−)-mandelic acid and (*S*)- and (*R*)-*p*-toluenesulfinamide, (R_S,2*R*)-(−)-**1**, (S_S,2*R*)-(+)-**4**, and (R_S,2*S*)-(−)-**4** were subjected to the phosphite addition reaction (Scheme 3).[3e] Under optimized conditions (KHMDS as base in THF solvent), the addition of dimethyl phosphite to (R_S,2*R*)-(−)-**1** resulted in 78% de exerting a match pair effect (Table 1, entry 8), while very low diastereomeric excesses, 26% and 30%, respectively, were observed in the cases of the (S_S,2*R*)-(+)-**4** and (R_S,2*S*)-(−)-**4** sulfinimines, which indicates a strong mismatch situation (Table 1, entries 9 and 10). In these examples, the reasonable assumption is made that the sense of stereoinduction is primarily determined by the sulfinyl group and β-hydroxy α-amino *N*-sulfinyl phosphonates **2** and **5** are the major products (Scheme 3).

As mentioned earlier, the addition of organometallic reagents to sulfinimines is controlled by the chirality of the sulfinyl group.[11] In the sulfinimine-mediated asymmetric Strecker synthesis, where diethylaluminum cyanide was added to sulfinimines (+)-**1**, (−)-**1**, (+)-**4**, and (−)-**4**, only a weak double stereodifferentiation effect was observed.[3c] For enantiomers (+)-(S_S,2*S*)-**1**/(−)-(R_S,2*R*)-**1**, which gave the same sense of stereoinduction as observed here, the de was >96%. For the missmatched pair, (S_S,2*R*)-(+)-**4**/(R_S,2*S*)-(−)-**4**, the de ranged from 74 to 86% de for cyanide addition. The present example, therefore, is unusual: the chirality of the sulfinyl is suppressed to a significant extent (26−30% de) by the resident chirality of the hydroxy group, resulting in a significant mismatch situation. While the origin of this effect is not well understood, at present we speculate that it results from the larger size and different structure of the metal phosphonate anion vs the cyanide reagent. Furthermore, the seven-membered twisted chairlike transition state **TS-1** (Scheme 2), proposed for phosphonate addition, is expected to be more conformationally mobile than the chelated six-membered chair transition state proposed for addition of organometallic reagents. This additional mobility may allow the chirality of the hydroxy moiety to have a greater influence on the stereoinduction.

The optimized methodology was next applied to the sulfinimines derived from (*S*)-(−)-**6** α-alkyl α-silyloxy aldehydes[13] and (*S*)-(+)-*p*-tolunesulfinamide (**7**) (Scheme 4). We were pleased to find that potassium dimethyl phosphite addition to these sulfinimines **8a**, **8b**, and **8c** proceeded in good yield, 74−75%, and with complete stereocontrol (>95% de). The expected matched pair affords the erythro isomers (S_S,1*R*,2*S*)-(+)-**9a**−**d** arising form the matched chirality resident in (+)-**8a**−**d** (Scheme 4).

The silyl protecting group could be removed by treatment of (+)-**9a** and (+)-**9b** with tetrabutylammonium fluoride (TBAF) at 0 °C without removing the *N*-sulfinyl group, which affords the β-hydroxy derivatives (+)-**10a** and (+)-**10b** in 66−67% yield (Scheme 4). With 3 N HCl

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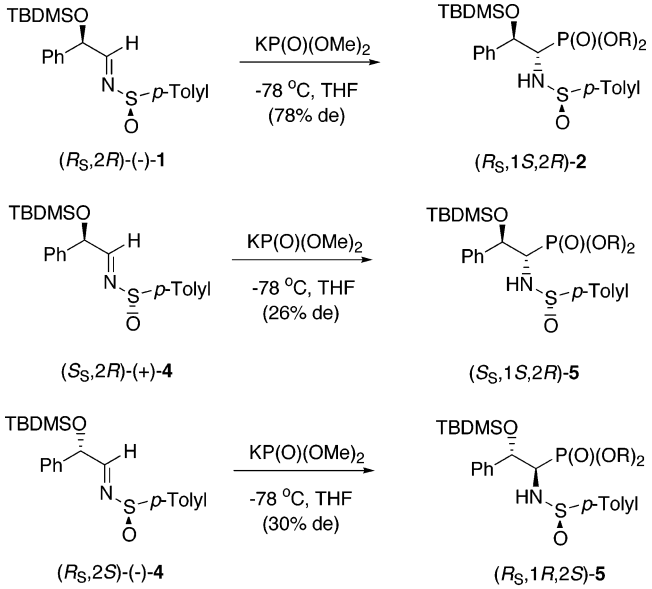
TABLE 1. Addition of Metal Dialkyl Phosphite to O-Protected α-Hydroxy Sulfinimines

entry	sulfinimines	phosphite (R′ =)	base/solvent	β-hydroxy *N*-sulfinyl α-amino phosphonate	dr[a]	% de	% yield
1	(S_S,2*S*)-(+)-**1**	Et	LiHMDS/THF	(S_S1*R*,2*S*)-**2**/(S_S,1*S*,2*S*)-**3**	77:23	54	
2		*i*-Pr	LiHMDS/THF		77:23	54	
3		Me	LiHMDS/THF		79:21	58	
4		Me	NaHMDS/THF		66:34	32	
5		Me	KHMDS/THF		93:7	86	71[b]
6		Me	KHMDS/toluene		88:12	76	
7		Me	KHMDS/Et_2O		89:11	78	
8	(R_S,2*R*)-(−)-**1**	Me	KHMDS/THF	(R_S1*S*,2*R*)-**2**/(R_S,1*R*,2*R*)-**3**	89:11	78	
9	(S_S,2*R*)-(+)-**4**	Me	KHMDS/THF	(S_S,1*R*,2*R*)-**5**/(S_S,1*R*,2*R*)-**6**	63:37	26	
10	(R_S,2*S*)-(−)-**4**	Me	KHMDS/THF	(R_S,1*S*,2*S*)-**5**/(R_S,1*R*,2*S*)-**6**	65:35	30	
11	(S_S,2*S*)-(+)-**8a** (Me)	Et	KHMDS/THF	(S_S,1*R*,2*S*)-(+)-**9a**	>97:3	>94	68
12	S_S,2*S*)-(+)-**8a** (Me)	Me	KHMDS/THF	(S_S,1*R*,2*S*)-(+)-**9b**	>97:3	>94	76
13	(S_S,2*S*)-(+)-**8b** (*i*-Pr)	Me	KHMDS/THF	(S_S,1*R*,2*S*)-(+)-**9c**	>97:3	>94	76
14	(S_S,2*S*)-(+)-**8c** (Bn)	Me	KHMDS/THF	(S_S,1*R*,2*S*)-(+)-**9d**	>97:3	>94	74

[a] Determined by ^{31}P NMR. [b] Isolated yield of the diastereoisomers mixture.

SCHEME 3



at reflux, (+)-**9b** gave the β-hydroxy α-amino phosphonate (+)-**11** in 72% yield, which is the phosphorus analogue of the amino acid threonine. Under these hydrolysis conditions, the phosphonate group remained intact. This finding is important because amino phosphonic acids are difficulty to work with given their limited solubility in aqueous and organic media. Hydrolysis of (+)-**11** in refluxing 6 N HCl provided the known β-hydroxy α-amino phosphonic acid (2*S*,3*S*)-(−)-**12** in 61% isolated yield.[8] This result provides convincing proof of our structure assignments of the major diastereoisomers **2**, **5**, and **9** as well as further validation for our hypothesized transition state, **TS-1** (Scheme 2). Interestingly, hydrolysis of the inseparable **2**/**3** mixture with 2 N HCl was unsuccessful and led to decomposition products. However, treatment with TBFA not only removed the *O*-silyl group, but the *N*-sulfinyl group as well, which afforded the phosphorus analogue of the amino acids threonine, (+)-**13**, in 50% yield as a single isomer following purification.

In conclusion, we have shown that the sulfinimines derived from α-hydroxy acids serve as excellent precursors for the preparation of erythro α-amino β-hydroxy phosphonic acids. A strong match−mismatch situation was observed in the addition of phosphite to the sulfinimines pseudoenantiomers.

Experimental Section

THF and diethyl ether were freshly distilled under argon from a purple solution of sodium and benzophenone. Unless stated otherwise, all the reagents were purchased from commercial sources and used without additional purification. α-Hydroxy sulfinimines (S_S,2*S*)-(+)-**1**,[3e] (R_S,2*R*)-(−)-**1**,[3e] (S_S,2*R*)-(+)-**4**,[3e] and (R_S,2*S*)-(−)-**4**,[3e] (*S*)-(−)-2-(*tert*-butyldimethylsilyloxy)propanal (**6a**),[13] (*S*)-(−)-2-*tert*-butyldimethylsilyloxy-3-methylbutanal (**6b**),[14] and (*S*)-(−)-2-(*tert*-butyldimethylsilyloxy)-3-phenylpropanal (**6c**)[14] were prepared as described previously.

General Procedure for the Synthesis of α-*tert*-Butyldimehtylsilyloxy Sulfinimines: (S_S,2*S*)-(+)-*N*-(2-*tert*-Butyldimethylsilyloxypropylidine)-*p*-toluenesulfinamide (8a). In two-neck, 100-mL, round-bottom flask equipped with a magnetic stirring bar, a rubber septa, and argon inlet was placed (−)-**6a** (0.19 g, 1 mmol) in CH_2Cl_2 (25 mL). A solution of (*S*)-(+)-*p*-toluenesulfinamide (**7**) (0.16 g, 1.1 mmol) in CH_2Cl_2 (10 mL) and $Ti(OEt)_4$ (1 mL, 5 mmol) were added successively, and the reaction mixture was stirred at rt for 3 h. The reaction mixture was cooled to 0 °C, quenched with ice−water (5 mL), and filtered through a pad of Celite, and the Celite pad was washed with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexane/ether 90:10) gave 0.17 g (52%) of a viscous oil: $[\alpha]^{20}_D$ = 190.4 (*c* 0.77, $CHCl_3$); IR (neat) 2930, 1632, 1472 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (d, *J* = 4.4 Hz, 1 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 4.51 (m, 1 H), 2.4 (s, 3 H), 1.36 (d, *J* = 6.5 Hz, 3 H), 0.85 (s, 9 H), 0.00 (s, 3H), −0.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.1, 142.09, 141.7, 130.2, 124.9, 70.8, 21.7, 26.11, 21.2, 18.5, −4.3, −4.5; HRMS calcd for $C_{16}H_{27}NO_2SiSNa$ (M + Na) 348.1429, found 348.1428.

(S_S,2*S*)-(+)-*N*-(2-*tert*-Butyldimethylsilyloxy-3-methylbutyrylidine)-*p*-toluenesulfinamide (8b). Chromatography (hexane/ether 90:10) afforded 0.34 g (48%) of a viscous oil and 0.024 g (11%) of **6b**: $[\alpha]^{20}_D$ = 226.4 (*c* 0.91, $CHCl_3$); IR (neat) 2957, 1634, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (d, *J* = 5.8 Hz, 1 H), 7.61 (d, *J* = 8.2 Hz, 2 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 4.13 (t, *J* = 5.7 Hz, 1 H), 2.46 (s, 3 H), 2.00 (octet, *J* = 6.7 Hz, 1 H), 0.99 (d, *J* = 6.8 Hz, 6 H), 0.88 (s, 9 H), 0.00 (s, 3 H), −0.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.9, 140.6, 140.2, 128.7, 123.4, 77.71, 24.2, 23.42, 20.41, 17.5, 17.1, 16.34; HRMS calcd for $C_{18}H_{31}NO_2SSiNa$ (M + Na) 354.1923, found 354.1918.

(S_S,2*S*)-(+)-*N*-(2-*tert*-Butyldimethylsilyloxy-3-phenylpropylidine)-*p*-toluene sulfinamide (8c). Chromatography

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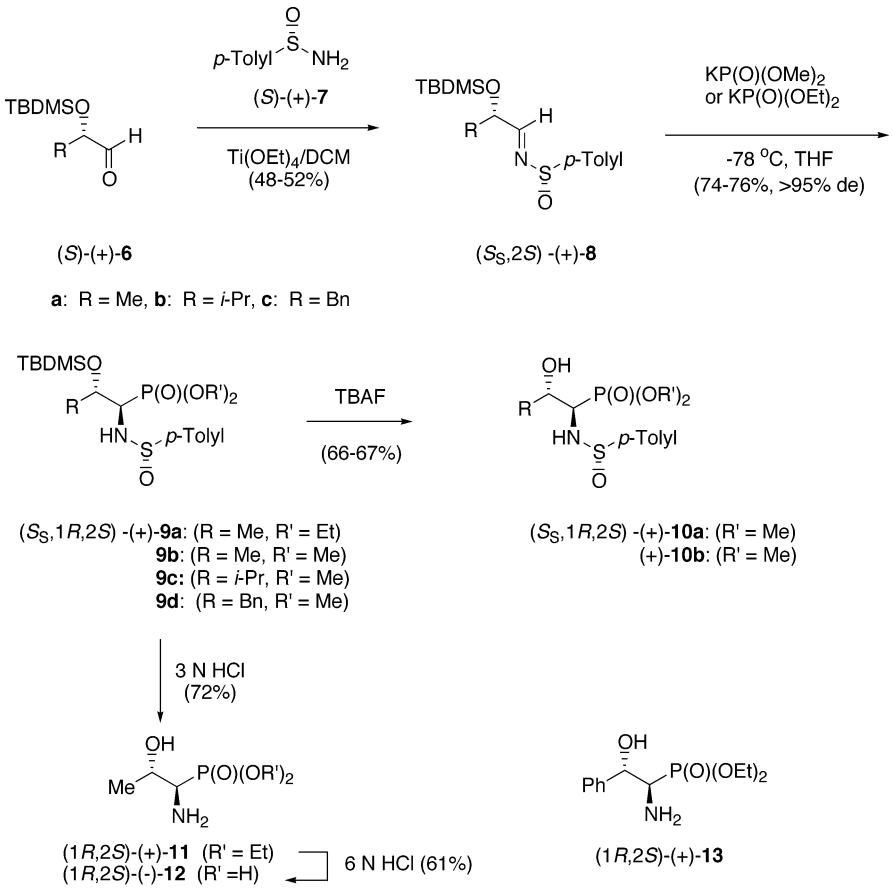
SCHEME 4



(hexane/ether 90:10) yielded 0.38 g (45%) of a viscous oil and 0.03 g (12%) of **6c**: $[\alpha]^{20}_D = 164.5$ (*c* 0.62, $CHCl_3$); IR (neat) 2928, 2856, 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.37 (d, $J = 5.0$ Hz, 1 H), 7.78 (d, $J = 8.1$ Hz, 2 H), 7.55−7.43 (m, 7 H), 4.76 (q, $J = 4.4$ Hz, 1 H), 3.23 (dd, $J = 4.2$, 13.4 Hz, 1 H), 3.10 (dd, $J = 8.8$, 13.4 Hz, 1 H), 2.66 (s, 3 H), 0.98 (s, 9 H), 0.00 (s, 3 H), −0.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.9, 142.2, 141.5, 137.4, 130.7, 130.2, 128.7, 127.0, 124.9, 75.9, 42.2, 26.1, 21.9, 18.4, −4.6, −5.1; HRMS calcd for $C_{22}H_{31}NO_2SSiNa$ (M + Na) 424.1742, found 424.1733.

General Procedure for the Addition of Dialkyl Phosphites to Sulfinimines: **(S_S,1*R*,2*S*)-(+)-Diethyl-1-(*p*-toluenesulfinylamino)-2-(*tert*-butyldimethylsilyloxy)propylphosphonate (9a).** In an oven-dried, two-neck, 50-mL, round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet were placed (+)-**8a** (0.33 g, 1 mmol) and diethyl phosphite (0.13 g, 1.2 mmol) in THF (20 mL). The solution was cooled to −78 °C, and KHMDS (1.2 mmol, 2.4 mL of 0.5 M solution in toluene) was added. After the mixture was stirred at −78 °C for 45 min, the reaction was complete as monitored by TLC. At this time, the reaction mixture was cooled to −78 °C, cautiously quenched with saturated NH_4Cl (5 mL), warmed to rt, and diluted with ether (40 mL). The organic layer was washed with water (2 × 20 mL) and brine (1 × 25 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexane/EtOAc/MeOH, 1:1:0.1) gave 0.31 g (68%) of a viscous mass: $[\alpha]_D = 52.6$ (*c* 0.77, $CHCl_3$); IR (neat) 3161, 2929, 1381, 1241, 1092 cm^{-1};^1H NMR ($CDCl_3$) δ 7.72 (d, $J = 8.4$ Hz, 2 H), 7.32 (d, $J = 8.6$ Hz, 2 H), 4.4 (dd, $J = 6.6$, 9.5 Hz, 1 H), 4.36 (m, 1 H), 4.29−4.03 (m, 4 H), 3.71 (ddd, $J = 2.6$, 9.5, 21.3 Hz, 1 H), 2.42 (s, 3 H), 1.4−1.26 (m, 6 H), 1.24 (d, $J = 6.6$ Hz, 3 H), 0.92 (s, 9 H), 0.02 (s 3 H), 0.0 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.0, 141.8, 130.0, 126.4, 70.1 (d, $J_{CP} = 14.7$ Hz), 63.6 (d, $J = 6.6$ Hz), 62.7 (d, $J = 6.6$ Hz), 58.0 (d, $J_{CP} = 149$ Hz), 54.1 (d, $J = 6.7$ Hz), 53.1 (d, $J = 6.6$ Hz), 26.2, 21.8, 20.1, 18.5, 16.8 (d, $J = 2.5$ Hz), −4.12, −4.37; ^{31}P NMR 21.8; HRMS calcd for $C_{20}H_{38}NO_5SiPSNa$ (M + Na) 486.1875, found 486.1886.

(S_S,1*R*,2*S*)-(+)-Dimethyl-1-(*p*-toluenesulfinylamino)-2-(*tert*-butyldimethylsilyloxy)propylphosphonate (9b). Chromatography (hexane/EtOAc/MeOH 1:1:0.1) gave 0.32 g (76%) of a white solid: mp 110−113 °C; $[\alpha]^{20}_D$ 67.2 (*c* 0.9, $CHCl_3$); IR (KBr) 3455, 3170, 2956, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (d, $J = 8.2$ Hz, 2 H), 7.15 (d, $J = 8.0$ Hz, 2 H), 4.47 (dd, $J = 5.7$, 9.6 Hz, 1 H), 4.21 (ddd, $J = 2.7$, 6.5, 13.9 Hz, 1 H), 3.63 (d, $J = 10.7$ Hz, 3 H), 3.52 (d, $J = 10.8$ Hz, 3 H), 2.26 (s, 3 H), 1.09 (d, $J = 6.4$ Hz, 3 H), 0.77 (s, 9 H), 0.00 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.4, 141.9, 129.8, 126.4, 70.0 (d, $J = 9.2$ Hz), 56.9 (d, $J_{CP} = 147$ Hz), 54.1 (d, $J = 6.7$ Hz), 53.1 (d, $J = 6.6$ Hz), 26.2, 21.7, 20.1, 18.5, −4.05, −4.4; ^{31}P NMR 23.9. Anal. Calcd for $C_{18}H_{34}NO_5PSSi$: C, 49.63; H, 7.87; N, 3.22. Found: C, 49.76; H, 8.04; N, 3.24.

(S_S,1*R*,2*S*)-(+)-Dimethyl-1-(*p*-toluenesulfinylamino)-2-(*tert*-butyldimethylsilyloxy)-3-methylbutylphosphonate (9c). Chromatography (hexane/EtOAc/MeOH 1:1:0.1) afforded 0.35 g (76%) of a white solid: mp 67−71 °C; $[\alpha]_D$ 67.2 (*c* 0.96, $CHCl_3$); IR (KBr) 3161, 2956, 1471 cm^{-1}; ^1H NMR 7.49 (d, $J = 8.2$ Hz, 2 H), 7.16 (d, $J = 8.1$ Hz, 2 H), 4.58 (dd, $J = 5.5$, 9.9 Hz, 1 H), 3.77 (ddd, $J = 2.2$, 7.6, 21.7 Hz, 1 H), 3.68−3.61 (m, 1 H), 3.56 (d, $J = 10.8$ Hz, 3 H), 3.46 (d, $J = 10.8$ Hz, 3 H), 2.27 (s, 3 H), 1.90 (m, 1 H), 0.80 (s, 9 H), 0.78 (d, $J = 6.8$ Hz, 3 H), 0.73 (d, $J = 6.8$ Hz, 3 H), 0.09 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR 142.0, 141.2 (d, $J = 1.7$ Hz), 129.4, 126.6, 81.4 (d, $J = 3.9$ Hz), 54.5 (d, $J_{CP} = 149.8$ Hz), 53.3 (d, $J = 7.0$ Hz), 53.2 (d, $J = 6.1$ Hz), 32.0, 26.6, 21.8, 21.1, 20.2, 18.8, −2.44, −4.02; ^{31}P NMR 25.0. Anal. Calcd for $C_{20}H_{38}NO_5PSSi$: C, 51.81; H, 8.26; N, 3.02. Found: C, 51.61; H, 8.40; N, 2.91.

(S_S,1*R*,2*S*)-(+)-Dimethyl-1-(*p*-toluenesulfinylamino)-2-(*tert*-butyldimethylsilyloxy)-3-phenylpropylphosphonate (9d). Chromatography (hexane/EtOAc/MeOH 1:1:0.1)

afforded 0.38 g (74%) of a viscous oil: $[\alpha]_D = 36.33$ (*c* 0.3, $CHCl_3$); IR (neat) 3167, 2955, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (d, $J = 8.2$ Hz, 1 H), 7.13−7.07 (m, 7 H), 4.67 (dd, $J = 4.8$, 10.1 Hz, 1 H), 4.46−4.34 (m, 1 H), 3.65 (d, $J = 10.8$ Hz, 3 H), 3.42 (d, $J = 10.8$ Hz, 3 H), 3.02 (dd, $J = 6.6$, 13.4 Hz, 1 H), 2.66 (dd, $J = 7.8$, 13.4 Hz, 1 H), 2.26 (s, 3 H), 0.78 (s, 9 H), 0.00 (s, 3 H), −0.29 (s, 3 H); ^{13}C NMR 141.7, 141.3 (d, $J = 1.5$ Hz), 138.5, 130.3, 129.7, 128.7, 126.8, 125.8, 76.5 (d, $J = 6.2$ Hz), 54.4 (d, $J_{CP} = 148.5$ Hz), 53.7 (d, $J_{CP} = 6.7$ Hz), 52.9 (d, $J_{CP} = 7.0$ Hz), 40.6, 26.2, 26.1, 21.6 (d, $J = 2$ Hz), 18.3, −4.1, −4.2; ^{31}P NMR 24.2; HRMS calcd for $C_{24}H_{38}NO_5SSiPNa$ (M + Na) 534.1875, found 534.1860.

(*S*S,1*R*,2*S*)-(+)-Dimethyl-1-(*p*-toluenesulfinylamino)-2-(*tert*-butyldimethylsilyloxy)-2-phenyethylphosphonate (2). Chromatography (hexane/EtOAc/MeOH 1:1:0.1) yielded 0.37 g (71%) of a mixture of 93:7 diastereomers. Major diastereomer: ^1H NMR ($CDCl_3$) δ 7.41 (d, $J = 8.2$ Hz, 2 H), 7.25 (m, 2 H), 7.17−7.07 (m, 5 H), 5.14 (dd, $J = 4.2$, 12.1 Hz, 1 H), 4.28 (dd, $J = 2.3$, 6.8 Hz, 1 H), 3.84 (ddd, $J = 4.3$, 9.6, 19.9 Hz, 1 H), 3.53 (d, $J = 10.7$ Hz, 3 H), 3.35 (d, $J = 10.7$ Hz, 3 H), 2.27 (s, 3 H), 0.88 (s, 3 H), 0.79 (s, 9 H), 0.00 (s, 3 H), −0.24 (s, 3 H); ^{13}C NMR δ 139.7, 139.5, 138.20, 127.3, 126.0, 125.7, 125.3, 123.6, 73.47 (d, $J = 7.6$), 57.1 ($J_{CP} = 149.7$ Hz), 55.6, 51.0 (d, $J = 6.7$ Hz), 50.6 (d, $J = 6.8$ Hz), 23.7, 19.2, 16.1, −6.8, −7.0; ^{31}P NMR 23.4; HRMS calcd for $C_{23}H_{36}NO_5SiPSNa$ (M + Na) 520.1719, found 520.1715.

General Procedure for the Synthesis of 1-(*p*-Toluenesulfinylamino)-2-hydroxy Phosphonates: (+)-(*S*S,1*S*,2*R*)-Dimethyl-1-(*p*-tolylsulfinylamino)-2-hydroxypropyl Phosphonates (10a). In an oven-dried, 25-mL, single-neck, round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed (+)-**9b** (0.43 g, 1 mmol) in THF (20 mL). The solution was cooled to 0 °C, and tetrabutylammonium flouride (1.2 mmol, 1.2 mL of 1 M solution in THF) was introduced. After the mixture was stirred at 0 °C for 3 h, the reaction was complete as indicated by TLC. At this time, the reaction mixture was diluted with cold ether (40 mL), washed successively with cold H_2O (40 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexane/EtOAc/MeOH: 1:1:0.1) gave 0.21 g (66%) as a white solid: mp 113−116 °C; $[\alpha]_D = 48.33$ (*c* 0.3, $CHCl_3$); IR (KBr) 3389, 3175, 1471 cm-1; ^1H NMR δ ($CDCl_3$) 7.47 (d, $J = 8.3$ Hz, 2 H), 7.24 (d, $J = 8.3$ Hz, 2 H), 5.02 (dd, $J = 3.3$, 10.7 Hz, 1 H), 4.62 (dd, $J = 1.2$, 11.8 Hz, OH exchangeable with D_2O), 3.89 (m, 1 H), 3.61 (d, $J = 10.8$ Hz, 3 H), 3.52 (d, $J = 10.8$ Hz, 3H), 3.30 (ddd, $J = 1.7$, 10.8, 23.9 Hz, 1 H), 2.33 (s, 3 H), 1.15 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) 142.7, 137.3, 130.2, 127.1, 64.7 (d, $J = 10$ Hz), 56.2 (d, $J_{CP} = 144$), 53.8 (d, $J = 6.9$ Hz), 53.4 (d, $J = 6.6$ Hz), 21.8, 19.0; ^{31}P NMR ($CDCl_3$) 23.9. Anal. Calcd for $C_{12}H_{20}NO_5PS$: C, 44.85; H, 6.27; N, 4.36. Found: C, 45.09; H, 6.06; N, 4.23.

(+)-(*S*S,1*S*,2*R*)-Dimethyl-1-(*p*-toluenesulfinylamino)-2-hydroxy-3-methylbutylphosphonate (10b). Chromatography (hexane/EtOAc/MeOH 1:1:0.1) gave 0.22 g (67%) as a white solid: mp 122−123 °C; $[\alpha]_D = 46.3$ (*c* 0.35, $CHCl_3$); IR (KBr) 3375, 3161, 2956, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) 7.48 (d, $J = 8.0$ Hz, 2 H), 7.23 (d, $J = 7.9$ Hz, 2H), 5.05 (dd, $J = 2.8$, 12.7 Hz, 1 H), 3.79 (dd, $J = 1.3$, 10.6 Hz, 1 H), 3.72 (dd, $J = 10.6$, 12.3 Hz, 1 H), 3.6 (d, $J = 10.7$ Hz, 3 H), 3.50 (d, $J = 10.7$ Hz, 3H), 2.33 (s, 3 H), 1.86 (m, 1 H), 0.93 (d, 6.6, 3 H), 0.86 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) 140.0, 137.6, 127.6, 124.1, 76.1, 51.8 (d, $J = 6.9$ Hz), 51.4 (d, $J = 6.9$ Hz) 50.7 (d, $J = 6.9$ Hz), 50.0, 29.0, 19.46, 17.9, 16.5; ^{31}P NMR ($CDCl_3$) 25.7. Anal. Calcd for $C_{14}H_{24}NO_5PS$: C, 48.13; H, 6.92; N, 4.01. Found: C, 48.04; H, 6.94; N, 3.90.

(1*R*,2*S*)-(+)-Diethyl-1-amino-2-hydroxy-2-phenylethylphosphonates (13). Chromatography (EtOAc/MeOH 1:0.1) gave 0.13 g (50%) as a viscous mass: $[\alpha]_D = 32.16$ (*c* 0.6 $CHCl_3$); IR (neat) 3373, 2983, 1602, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.22 (m, 5 H), 4.72 (dd, $J = 7.7$, 12.2 Hz, 1H), 4.11−3.94 (m, 4H), 3.17 (dd, $J = 7.7$, 13.2 Hz, 1H), 2.4 (broad, 1 H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.20 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.5, 138.4, 126.6, 126.4, 125.3, 73.1, 60.9 (d, $J = 6.9$ Hz), 60.8 (d, $J = 7.2$ Hz), 52.4 (d, $J_{CP} = 149$ Hz), 14.6 (t, $J = 6.5$ Hz); ^{31}P NMR 26.9; HRMS calcd for $C_{12}H_{21}NO_4P$ (M + H) 274.1208, found 274.1206.

(1*R*,2*S*)-(+)-Diethyl-1-amino-2-hydroxypropylphosphonate (11). In a single-neck, round-bottomed flask fitted with a magnetic stirring bar was placed (+)-**9a** (0.32 g, 1 mmol) in MeOH (10 mL). Hydrochloric acid (3 N, 5 mL) was added, and the reaction mixture was refluxed for 8 h. At this time, the reaction mixture was concentrated and the residue was neutralized to pH 8 by addition of aqueous NH_4OH. Enough solid NaCl was then added to saturate the solution, which was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (EtOAc/MeOH 1:0.2) afforded 0.15 g (72%) of an oil: $[\alpha]_D = 5.89$ (*c* 0.56 $CHCl_3$); IR (neat) 3383, 2982, 1224 cm^{-1}; ^1H NMR ($CDCl_3$) 4.13−4.07 (m, 4 H), 3.90 (dq, $J = 6.2$, 11.5 Hz, 1 H), 2.90 (dd, $J = 6.0$, 13.7 Hz, 1 H), 1.27 (t, $J = 7.1$ Hz, 6 H), 1.21 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR ($CDCl_3$) 68.1 (d, $J = 6.3$ Hz), 62.8 (d, $J = 6.9$ Hz), 62.6 (d, $J = 7.2$ Hz), 54.1 (d, $J_{CP} = 143.8$ Hz), 19.8 (d, $J = 6.5$ Hz), 16.9; ^{31}P NMR ($CDCl_3$) 27.3; HRMS calcd for $C_7H_{19}NO_4P$ (M + H) 212.1052, found 212.1051.

(1*R*,2*S*)-(−)-1-Amino-2-hydroxypropylphosphonic Acid Hydrochloride (12). In a single-neck, 50-mL, round-bottom flask equipped with a reflux condenser was placed (+)-**11** (0.052 g, 0.25 mmol) in EtOH (5 mL), and 6 N HCl (25 mL) was added. The reaction mixture was reflux for 18 h, cooled to rt, and concentrated. The residue was washed with ether (2 × 25 mL), H_2O (10 mL) was added, and the solution was passed through a short plug of Celite. Evaporation of the aqueous phases gave 0.025 g (61%) of a viscous mass: $[\alpha]_D = -5.6$ (*c* 0.8 D_2O) (lit.[15] $[\alpha]_D = -6.9$ (*c* 0.67 D_2O). The spectral properties are consistent with those reported in the literature.[15]

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Supporting Information Available: General procedures and spectral data for compounds where only HRMS is available. This material is available free of charge via the Internet at http://pubs.acs.org.

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