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Use of optically active cyclic diethyl sulfamidate 2-phosphonates as chiral synthons for the synthesis of β-substituted α-amino phosphonates

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Abstract—Optically active protected sulfamidate 2-phosphonates have been synthesized from either (*R*)- or (*S*)-*N*-benzyl-2-phosphonoserine for use as chiral synthons. These sulfamidates have been shown to undergo nucleophilic substitution with select nucleophiles, to afford following *N*-sulfate removal, the β-substituted α-amino-2-phosphonates. *N*-Sulfate removal was accomplished using boron trifluoride etherate in the presence of either *n*-propylthiol or *N*-hydroxysuccinimide allowing retention of the diethylphosphonate ester groups. Replacement of the unpleasant smelling *n*-propylthiol with *N*-hydroxysuccinimide provides higher yields of the desired products. Synthesis of β-*S*-substituted analogues required the use of cesium carbonate as a base. The sulfamidates described have excellent stability and have been demonstrated, using chiral HPLC, to be greater than 97% enantiomerically pure.

1. Introduction

Proteases play critical roles physiologically in a number of disease states including arthritis, Alzheimer's disease, osteoporosis, cancer cell invasion, viral infections, the apoptosis process, while their rich chemistry has been recently reviewed.[18,19,33,44] Medicinally, α-amino-α-alkylphosphonic acids and their analogues including phosphinic acids show promise as potential protease inhibition agents in addition to pesticidal and herbicidal activity.[23,29,39] Substitution of the amino acid carboxyl group with a phosphonate group has produced organophosphonate analogues of nearly all the natural amino acids.[8] The synthesis of phosphonopeptides from the α-amino-α-alkylphosphonic acids has resulted in the production of tetrahedral transition state analogue inhibitors of a variety of natural protease enzymes.[4,5] However, with the increasing focus on the enantiomeric purity of drugs in the pharmaceutical industry, there is a need for methodology to synthesize enantiopure α-amino-α-alkylphosphonic acids with various unnatural sidechains. Although numerous methods exist[1–3,6,9–15,17,21,22,25–27,31,32,34–37,42,43,45] for the synthesis of both racemic and enantioenriched compounds, there is still room for improvement in methodology that can rapidly produce a variety of side chain analogues from a common chiral precursor molecule such as a chiral synthon. This is especially important if a combinatorial approach is needed to generate a large number of compounds rapidly. This laboratory has investigated[16] the nucleophilic substitution of enantiomerically enriched *N*-tosyl aziridine 2-phosphonates as a chiral synthon for this approach and found it to be useful but with a significant limitation. This limitation involves the often difficult to remove *N*-tosyl group, in which only a dissolving sodium metal reduction in liquid ammonia proved successful in removing this protecting group with the amino phosphonates we have studied. Herein we report the use of chiral sulfamidates as a chiral synthon with the easily removable *N*-benzyl protecting group and determine what advantages they may possess with respect to nucleophilic attack by common nucleophiles. Melendez and Lubell have recently reviewed[30] both sulfamidite and sulfamidate chemistry.

2. Results and discussion

The key starting materials, the highly enantioenriched (*R*)- and (*S*)-phosphonoserines, were independently

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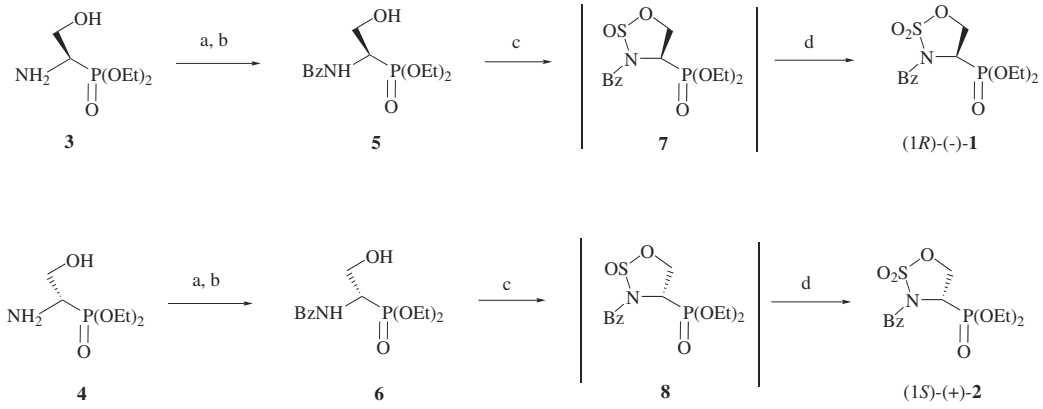
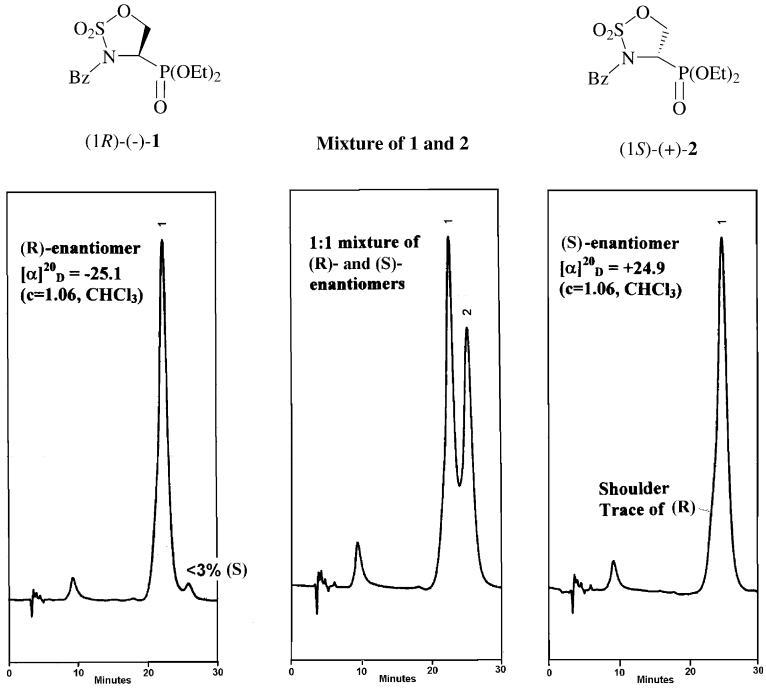
produced using the method reported by Smith et al.[40,41] A large scale synthesis of these two enantiopodes has been described in detail in our previous report.[16] Each phosphonoserine enantiomer was independently carried forward to the sulfamidates **1** and **2** as described in Scheme 1. Treatment of the amino alcohols **3** and **4** with benzaldehyde followed by reduction with sodium cyanoborohydride in ethanol and acetic acid afforded the *N*-benzyl amines **5** and **6** in 70% and 64% yield, respectively. Conversion of **5** and **6** to the sulfamidates was accomplished by the method of Wei and Lubell[46] involving dropwise treatment with a solution of thionyl chloride in chloroform in the presence of triethylamine and imidazole. This produced **7** and **8** as equal mixtures of diastereomers at the sulfamidite stereocenter as observed by NMR spectroscopy. These crude reaction mixtures were directly subjected to ruthenium chloride catalyzed periodate oxidation converting the sulfamidites to sulfamidates **1** and **2** in 70% and 63% yields, following flash silica chromatography. This conversion required monitoring by ^{31}P NMR since the sulfamidites and sulfamidates did not separate on silica thin-layer chromatography. Additionally to ensure successful conversion, the ruthenium chloride was ground to a fine powder prior to use.

The enantiomeric purity of the sulfamidates **1** and **2** was established using Whelk O-2 chiral HPLC as depicted in Scheme 2. The specific rotations of the sulfamidates **1** and **2** were determined to be −25.1 and +24.9, respectively, and in each case chiral HPLC confirmed an enantiomeric excess of at least 97%. These two sulfamidate oils proved to be very stable when stored for up to a year at −20 °C.

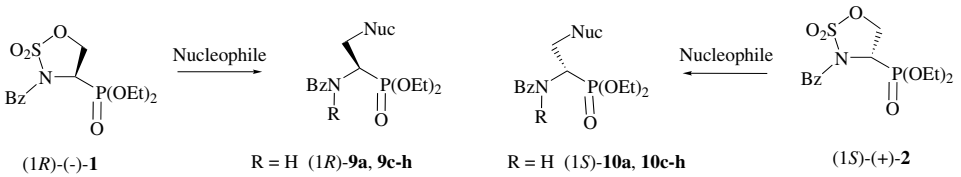


Scheme 1. Synthesis of the (1*R*)-(−)- and (1*S*)-(+)-sulfamidates **1** and **2**. Reagents: (a) PhCHO, EtOH, HOAc; (b) $NaCNBH_3$; (c) $SOCl_2$, imidazole, Et_3N, CH_2Cl_2; (d) $RuCl_3$, $NaIO_4$, aqueous CH_3CN.



Scheme 2. Whelk O-2 chiral HPLC of the sulfamidates **1** and **2** (retention times: (1*R*)-(−)-**1**: t_R = 22.73 min, (1*S*)-(+)-**2**: t_R = 25.02 min).

Table 1. Reaction of (1*R*)-(−)- and (1*S*)-(+)-sulfamidates **1** and **2** with nucleophiles



(1*R*)-(-)-**1** R = H (1*R*)-**9a**, **9c-h** R = SO_3^- (1*R*)-**9b** R = H (1*S*)-**10a**, **10c-h** R = SO_3^- (1*S*)-**10b** (1*S*)-(+)-**2**

Nucleophile	Product	Isolated yield (%)	$[\alpha]_D^{20}$
NaCN, DMF	**9a**	30 (51[a])	−11.2 (*c* 0.760)
	10a	42 (77[a])	+10.2 (*c* 0.760)
Phenethylamine, THF	**9b**	64	−46.3 (*c* 0.640)
	10b	50	+46.4 (*c* 0.724)
	9c	79	−17.7 (*c* 0.608)
	10c	79	+18.5 (*c* 0.840)
Imidazole, THF	**9d**	23 (38[a])	−26.0 (*c* 0.238)
	10d	25	+26.0 (*c* 0.266)
N-Hydroxysuccinimide, Et_3N, CH_3CN	**9e**	72	−6.6 (*c* 0.802)
	10e	76	+6.5 (*c* 0.840)
$NaBH_4$, THF	**9f**	35 (84[a])	−6.0 (*c* 0.212)
	10f	64	+6.2 (*c* 0.422)
n-PrSH, Cs_2CO_3, DMF	**9g**	57	−90.3 (*c* 0.568)
	10g	71	+84.9 (*c* 0.708)
2-Naphthalenethiol, Cs_2CO_3, DMF	**9h**	79	−81.2 (*c* 0.894)
	10h	70	+83.6 (*c* 0.860)

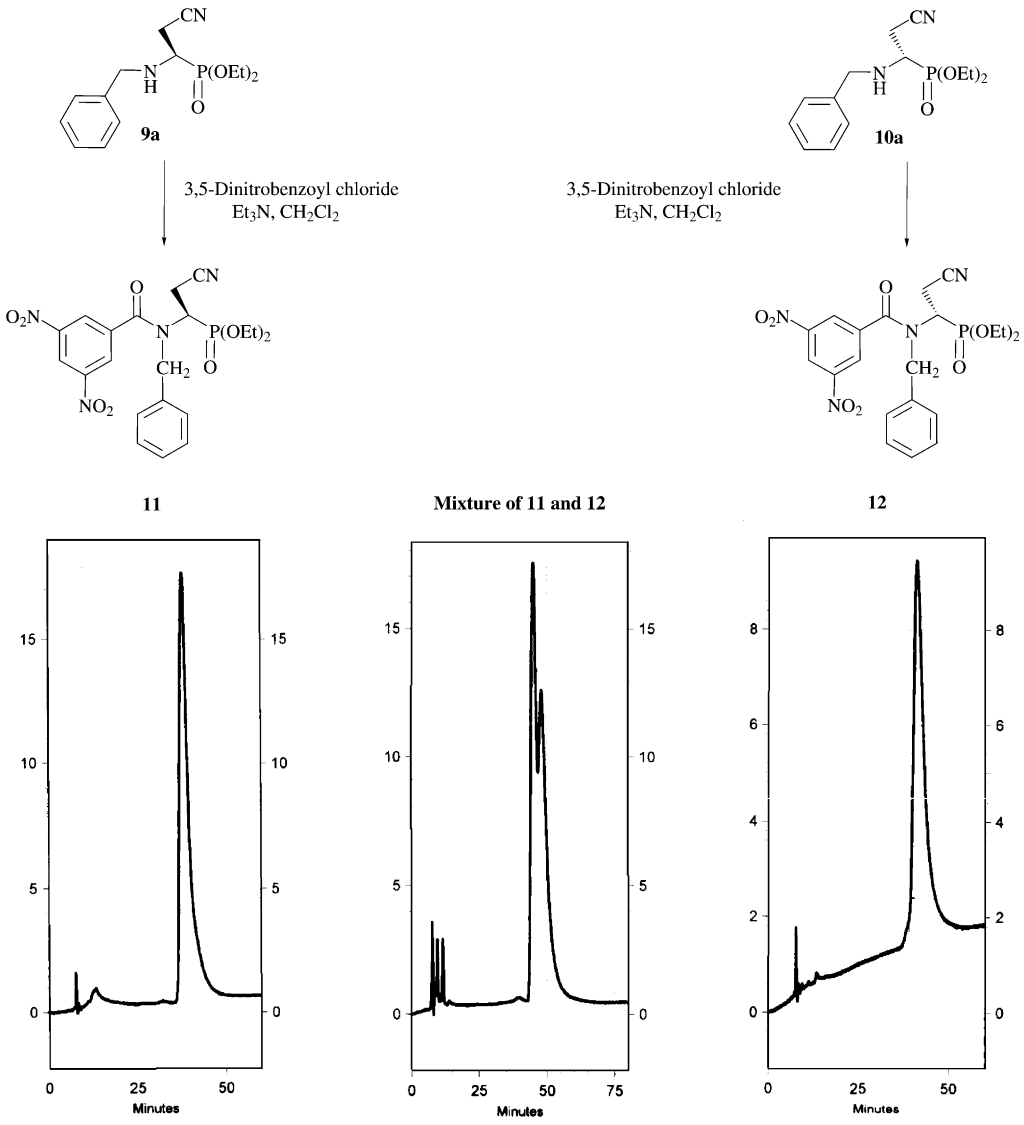
[a] Product yield afforded using *N*-hydroxysuccinimide/boron trifluoride etherate to remove the *N*-sulfate.

Reaction of the sulfamidates with a variety of nucleophiles is shown in Table 1. A number of methods[30] for the removal of the *N*-sulfate group that results following nucleophilic attack at the β-position are available, however most are highly acidic involving protic acids or the Lewis acid boron trifluoride etherate. In order to preserve the phosphonate ethyl groups we have utilized the boron trifluoride etherate and *n*-propylthiol method of Kim and So.[24]

Carbon nucleophiles such as cyanide, react with the sulfamidates to provide the nitrile products **9a** and **10a** in modest yield ranging from 30% to 42%, respectively, utilizing the boron trifluoride etherate and thiol method for *N*-sulfate removal. Malonate anion produced modest amounts of product but rapidly decomposed. Use of *N*-hydroxysuccinimide as the nucleophile and triethylamine as a base afforded good yields of products **9e** (76%) and **10e** (72%). Reduction of the sulfamidates with $NaBH_4$ provided the methyl analogues **9f** and **10f** in 35% and 64% yields, respectively. The amino nucleophiles phenethylamine (Scheme 4) and imidazole provided lower yields than expected, as reported in Table 1. The results from the *N*-hydroxysuccinimide reaction suggest that the lower product yields were not caused by removal[28,38] of an alkyl group from the phosphonate moiety by the boron trifluoride etherate and thiol method. This led us to speculate that *N*-hydroxysuccinimide may serve as an effective nucleophile in the removal of the *N*-sulfate group. A number of the reactions were repeated by substituting *N*-hydroxysuccinimide for the foul smelling *n*-propylthiol. In each case, as reported in Table 1, *N*-sulfate removal occurred increasing yields from 15% to 30% for the reactions investigated.

Chiral HPLC, to confirm enantiopurity directly on the *N*-benzylamine isolated products using a Whelk O-2 chiral column, was plagued by long retention times and severe broadening, despite the addition of additives to the mobile phase. Derivatization as the *N*-benzyl-*N*-3,5-dinitrobenzoyl analogue and analysis conducted using a Pirkle (*S*)-Leu and (*R*)-NEA chiral phase proved useful as depicted for **9a** and **10a** in Scheme 3. Although conversion to **11** and **12** afforded incomplete baseline separation and long retention times, it established that extensive racemization had not occurred during the nucleophilic ring opening or the subsequent *N*-sulfate removal process.

It was observed that the boron trifluoride etherate mediated thiol method fails to successfully remove the *N*-sulfate group in the case of the phenethylamine adducts (Scheme 4). Using *n*-propylthiol, the *N*-sulfate products **9b** and **10b** (zwitterionic) were isolated by silica gel chromatography. Electrospray ionization mass spectroscopy produced identical spectra for **9b**, **10b**, **9c**, and **10c** in the mass range of 0–750 mass units although the ^1H NMR spectra for **9b** and **10b** were different from the reaction products **9c** and **10c** using *N*-hydroxysuccinimide. During ESI-MS analysis, **9b** and **10b** easily lose SO_3 and

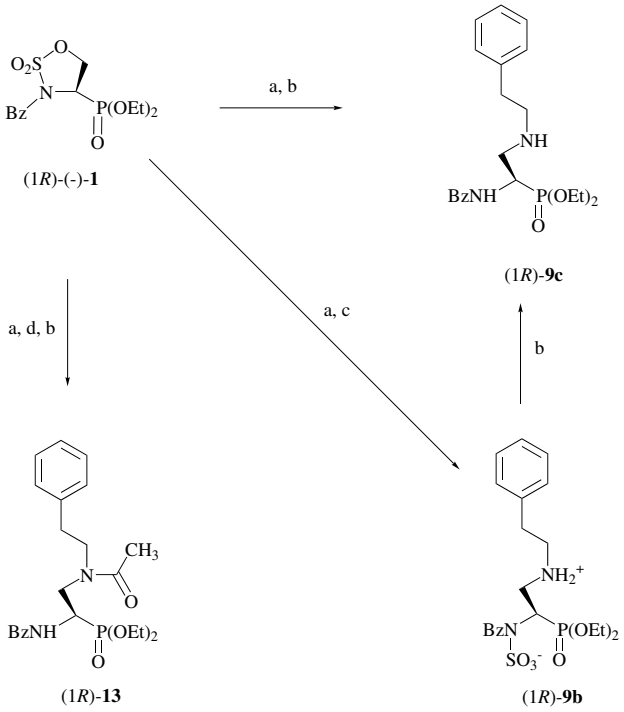


Scheme 3. Derivatization of **9a** and **10a** and Pirkle phase chiral HPLC of **11** and **12** (retention times: (1*R*)-(−)-**11**: t_R = 44.98 min, (1*S*)-(+)-**22**: t_R = 47.98 min).

afforded *m*/*z* peaks of 391.1 ($M-SO_3+H$) and 413.1 ($M-SO_3+Na$). Reacquisition of the ESI-MS for **9b** in the mass range of *m*/*z* 0–2000 revealed the additional ion clusters: 2M + Na (*m*/*z* 963.0), 3M + Na (*m*/*z* 1432.9), and 4M + Na (1902.7). The ^{13}C NMR revealed only slight differences in the benzylic methylene carbon chemical shift values at 50.6 ppm (amine) versus 49.2 ppm (*N*-sulfate). The ^{31}P NMR chemical shifts were significantly different (27.4 ppm for **9c** and **10c** and 19.7 ppm for **9b** and **10b**). Further evidence supporting the *N*-sulfate adduct for **9b** and **10b** was observed in the IR spectra with a broad signal ranging from 3300 to 2500 cm^{-1} (zwitterionic) and a strong 1175 cm^{-1} band for the organic $N\text{-}SO_3^-$ functional group, which was absent in the IR for **9c** and **10c**.

The stability of a *N*-sulfate group following reaction with a primary amine offers an opportunity to use it as a temporary blocking group to allow further differentiation of the amino nucleophile nitrogen as depicted in Scheme 4. Treatment of the sulfamidate **1** with phenethylamine followed by acetic anhydride and *N*-sulfate removal using boron trifluoride etherate and *N*-hydroxysuccinimide produced a 69% yield of the *N*-acetyl derivative **13** (^{31}P NMR 26.06 ppm). This should provide a useful method to expand upon the diversity of side chains in the β-amino substituted α-aminophosphonates.

Cesium carbonate proved to be a superior base for the reaction of thiols with the sulfamidates **1** and **2**. Following the method reported by Boulton et al.[7] exposure of the sulfamidates to 2 equiv of *n*-propylthiol or 2-naphthalenethiol and Cs_2CO_3 in DMF for 2 h followed by *N*-sulfate removal afforded the thiol adducts **9g**, **10g**, **9h**, and **10h** cleanly in 57–79% isolated yield. Use of tri-*n*-butylphosphine[20] in the presence of 2-naphthalenethiol in refluxing acetonitrile afforded only 36% yield of **9h**. Boron trifluoride etherate in the presence of thiol at reflux in acetonitrile failed to produce any trace of desired



Scheme 4. Reaction of **1** with phenethylamine and the boron trifluoride etherate mediated *N*-sulfate removal to afford **9b** and **9c** and selective *N*-modification to afford **13**. Reagents: (a) phenethylamine, THF; (b) boron trifluoride etherate, *N*-hydroxysuccinimide, CH_2Cl_2; (c) boron trifluoride etherate, *n*-propylthiol, CH_2Cl_2; (d) CH_2Cl_2, Et_3N, Ac_2O.

product. Additionally, the sulfamidates failed to produce useful adducts by reaction with sodium iodide in acetone, tetrabutylammonium fluoride in THF, or trimethylphosphite in THF. The sulfamidate **1** would react with methanol at reflux in the presence of excess boron trifluoride etherate to produce the β-*O*-methyl analogue (31% yield) but only after very long reaction times. Refluxing methanol in the presence of triethylamine, tri-*n*-butylphosphine or Cs_2CO_3 failed to produce any β-*O*-methyl products.

3. Conclusion

In summary, we have demonstrated that *N*-benzyl sulfamidate 2-phosphonates **1** and **2** are stable, useful and highly enantioenriched chiral synthons. The rapid synthesis of β-substituted α-aminophosphonates was accomplished by facile reaction of **1** and **2** with carbon, amino, hydride, oxygen, and sulfur nucleophiles. Successful removal of the *N*-sulfate group was achieved in difficult cases, such as the phenethylamine adduct by using boron trifluoride etherate and *N*-hydroxysuccinimide, while preserving the *O*-ethyl groups of the phosphonate. In the case of a primary amino nucleophile, the *N*-sulfate group can act further as a temporary blocking group to allow acylation at the β-amino group. Further work in the area of β-*O*-alkyl adducts by reaction with alcohols and other nucleophiles is in progress and will be reported in due course.

4. Experimental

4.1. General

The solvent 1,2-dichloroethane, $NaBH_4$, and other chemicals were purchased from Acros/Fisher or Aldrich Chemical Company. THF was distilled from sodium benzophenone, Et_3N, CH_3CN, and CH_2Cl_2 were distilled from CaH_2. DMF was vacuum distilled from CaH_2. $CHCl_3$ for the reactions was distilled from P_2O_5. EtOAc and hexanes were distilled prior to use. All reactions and distillations were conducted under an inert nitrogen atmosphere. Analytical thin-layer chromatography was carried out on E. Merck precoated silica gel 60 (0.2 mm, aluminum or glass support) TLC plates. Preparative TLC including radial chromatography was carried out using E. Merck silica gel 60. Flash silica gel column chromatography was carried out using Mallinckrodt silica gel 60, 230–400 mesh. Chiral HPLC was carried out using a Regis (*S*,*S*) Whelk O-2 250×4.60 mm column or a Phenomenex® Chirex (*S*)-Leu and (*R*)-NEA 250×4.60 mm column with monitoring at 254 nm. All HPLC solvents were filtered through a 0.45 μm filter prior to use. The term 'dried' refers to drying of a solution over anhydrous magnesium sulfate. Distilled deionized water was obtained from a Millipore NanoPure system. ^1H, ^{13}C, and ^{31}P NMR spectra were obtained using a Bruker Avance 400 MHz NMR and were referenced to either TMS or the residual NMR solvent signal for d_6-DMSO at 2.50 ppm for ^1H or 39.5 ppm for ^{13}C. ^{31}P NMR was subject to external reference using H_3PO_4 at 0.00 ppm. Optical rotations were obtained in spectral grade solvents using a Perkin–Elmer 341 polarimeter. Infrared spectra were obtained as thin films on NaCl plates using a Perkin–Elmer 457 spectrophotometer. Electrospray mass spectra were obtained on a Finnigan electrospray mass spectrometer located in the University of Wyoming Department of Chemistry using a solution of 1:1 acetonitrile–water containing 0.1% trifluoroacetic acid or in methanol and water.

4.2. General procedure for *N*-benzylation of amino alcohols 3 and 4

4.2.1. Diethyl (1*R*)-(1-(*N*-benzylamino))-2-hydroxyethyl phosphonate 5. To a solution of amino alcohol **3** (1.11 g, 5.605 mmol) in 22 mL of absolute EtOH was added glacial acetic acid (0.60 mL, 11.210 mmol) followed by benzaldehyde (0.654 g, 6.165 mmol) and sodium cyanoborohydride (0.528 g, 8.400 mmol). This solution was stirred under N_2 for 18 h. Solid $NaHCO_3$ (1.41 g, 16.80 mmol) was added and the EtOH was removed in vacuo. To the residue was added 50 mL of water followed by extraction with two 50 mL portions of CH_2Cl_2. The pooled organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo to afford 1.41 g of a clear oil. This oil was purified by column chromatography using 120 mL volume of silica eluting with 1:10 MeOH–$CHCl_3$ to afford 1.118 g (70% yield) of **5** as a clear oil: $[\alpha]_D^{20} = -23.8$ (*c* 0.800, $CHCl_3$); IR (TF) 3350, 3040, 2995, 2960, 1610, 1502, 1460, 1400, 1375, 1230, 1045, 975, 795, 750, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32–1.37 (m, 6H, CH_3), 2.98–3.07 (m, 1H,

CHP), 3.68–3.83 (m, 2H, $PCHCH_2OH$), 3.84–4.02 (m, 2H, benzylic CH_2), 4.10–4.23 (m, 4H, $POCH_2$), 7.22–7.37 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.44 (t, J_{CCOP} = 5.7 Hz, CH_3CH_2OP), 52.02 (d, J_{CCP} = 6.8 Hz, $HOCH_2CHP$), 55.70 (d, J_{CP} = 146.9 Hz, CHP), 60.09 (d, J_{CNCP} = 4.4 Hz, benzylic CH_2), 62.09 (d, J_{COP} = 6.9 Hz, CH_3CH_2OP), 62.42 (d, J_{COP} = 6.8 Hz, CH_3CH_2OP), 127.20, 128.23, 128.38, 139.40; ^{31}P NMR ($CDCl_3$): δ 26.77. Positive ion ESMS: calculated: $C_{13}H_{23}O_4N_1P_1$ *m/z* (M+H) 288.1. Found: $C_{13}H_{23}O_4N_1P_1$ *m/z* (M+H) 288.1 (100%).

4.2.2. Characterization data for diethyl (1*S*)-(1-(*N*-benzylamino))-2-hydroxyethyl phosphonate 6. Yield 64%; $[\alpha]_D^{20} = +20.0$ (*c* 0.226, $CHCl_3$); IR (TF) 3350, 3040, 2995, 2960, 1610, 1502, 1460, 1400, 1375, 1230, 1045, 975, 795, 750, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32–1.37 (m, 6H, CH_3), 2.98–3.07 (m, 1H, CHP), 3.68–3.83 (m, 2H, $PCHCH_2OH$), 3.84–4.02 (m, 2H, benzylic CH_2), 4.10–4.23 (m, 4H, $POCH_2$), 7.22–7.37 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.44 (t, J_{CCOP} = 5.7 Hz, CH_3CH_2OP), 52.02 (d, J_{CCP} = 6.8 Hz, $HOCH_2CHP$), 55.70 (d, J_{CP} = 146.9 Hz, CHP), 60.09 (d, J_{CNCP} = 4.4 Hz, benzylic CH_2), 62.09 (d, J_{COP} = 6.9 Hz, CH_3CH_2OP), 62.42 (d, J_{COP} = 6.8 Hz, CH_3CH_2OP), 127.20, 128.22, 128.38, 139.36; ^{31}P NMR ($CDCl_3$): δ 26.54. Positive ion ESMS: calculated: $C_{13}H_{23}O_4N_1P_1$ *m/z* (M+H) 288.1. Found: $C_{13}H_{23}O_4N_1P_1$ *m/z* (M+H) 288.1 (100%).

4.3. General procedure for the synthesis of sulfamidates 1 and 2

4.3.1. Diethyl ((4*R*)-3-benzyl-1,2,3-oxathiazolidine 2,2-dioxide)-4-phosphonate 1. To a solution of amino alcohol **5** (0.897 g, 3.114 mmol), imidazole (0.849 g, 12.450 mmol), Et_3N (0.630 g, 6.227 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added dropwise 2 M thionyl chloride in $CHCl_3$ (1.71 mL, 3.425 mmol). This mixture was stirred for 30 min followed by transfer to a separatory funnel with the aid of 50 mL of CH_2Cl_2 and 20 mL of water. The aqueous phase was extracted with two 20 mL portions of CH_2Cl_2. The pooled organic layers were washed with three 25 mL portions of water, brine, dried, filtered, and evaporated in vacuo to afford 1.108 g of crude **7** as a clear oil. To this oil was added 90 mL of CH_3CN and cooled to 0 °C. Powdered $RuCl_3$ (0.010 g, 0.048 mmol) and $NaIO_4$ (1.33 g, 6.227 mmol) were added followed by the dropwise addition of 90 mL of water over 30 min. The mixture was stirred overnight while warming to room temperature. The CH_3CN was evaporated in vacuo and the solution transferred to a separatory funnel and extracted with three 50 mL portions of Et_2O. The pooled organic phases were washed with 50 mL of saturated aqueous $NaHCO_3$, brine, dried, filtered, and evaporated in vacuo. The residue was purified by column chromatography using a 70 mL volume of silica eluting with 1:20 MeOH–$CHCl_3$ to afford 0.766 g of **1** (70% yield) as a clear oil. $[\alpha]_D^{20} = -25.1$ (*c* 1.06, $CHCl_3$); IR (TF) 3040, 2995, 2960, 1602, 1460, 1450, 1355, 1245, 1195, 1020 (br), 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32–1.38 (m, 6H, CH_3), 3.79 (t, J = 7.2 and 7.5 Hz, 1H, CHP), 4.14–4.31 (m, 4H, $POCH_2$), 4.43 (d, 1H, J = 14.6 Hz, diastereotopic benzylic CH_2), 4.54–4.60 (m, 2H, $PCHCH_2OS$), 4.66 (d, 1H, J = 14.6 Hz, diastereotopic benzylic CH_2), 7.30–7.40 (m, 3H, aromatic H), 7.47–7.51 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.28 (d, J_{CCOP} = 5.7 Hz, CH_3CH_2OP), 16.41 (d, J_{CCOP} = 5.4 Hz, CH_3CH_2OP), 51.61, 54.16 (d, J_{CP} = 172.3 Hz, CHP), 62.97 (d, J_{COP} = 6.9 Hz, CH_3CH_2OP), 64.47 (d, J_{COP} = 6.7 Hz, CH_3CH_2OP), 65.28, 128.48, 128.60, 129.59, 133.58; ^{31}P NMR ($CDCl_3$): δ 16.99. Positive ion ESMS: calculated: $C_{13}H_{20}N_1P_1S_1O_6Na_1$ *m/z* (M+Na) 372.1. Found: $C_{13}H_{20}N_1P_1S_1O_6Na_1$ *m/z* (M+Na) 372.1 (100%); Chiral HPLC using a WHELK O-2 column eluting with 10:120:40 2-propanol–hexanes–1,2-dichloroethane at 1 mL/min afforded 97.4% (*R*)-enantiomer (t_R = 22.73 min) and 2.6% of the contaminating (*S*)-enantiomer (t_R = 25.02 min).

4.3.2. Characterization data for diethyl ((4*S*)-3-benzyl-1,2,3-oxathiazolidine 2,2-dioxide)-4-phosphonate 2. Yield 63%; $[\alpha]_D^{20} = +24.9$ (*c* 1.06, $CHCl_3$); IR (TF) 3040, 2995, 2960, 1602, 1460, 1450, 1355, 1245, 1195, 1020 (br), 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32–1.38 (m, 6H, CH_3), 3.80 (t, J = 7.2 and 7.4 Hz, 1H, CHP), 4.14–4.31 (m, 4H, $POCH_2$), 4.43 (d, 1H, J = 14.6 Hz, diastereotopic benzylic CH_2), 4.54–4.60 (m, 2H, $PCHCH_2OS$), 4.67 (d, 1H, J = 14.6 Hz, diastereotopic benzylic CH_2), 7.30–7.40 (m, 3H, aromatic H), 7.47–7.51 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.29 (d, J_{CCOP} = 5.5 Hz, CH_3CH_2OP), 16.42 (d, J_{CCOP} = 5.4 Hz, CH_3CH_2OP), 51.61, 54.13 (d, J_{CP} = 172.7 Hz, CHP), 62.97 (d, J_{COP} = 7.1 Hz, CH_3CH_2OP), 64.50 (d, J_{COP} = 6.9 Hz, CH_3CH_2OP), 65.27, 128.49, 128.61, 129.55, 133.55; ^{31}P NMR ($CDCl_3$): δ 17.00. Positive ion ESMS: calculated: $C_{13}H_{20}N_1P_1S_1O_6Na_1$ *m/z* (M+Na) 372.1. Found: $C_{13}H_{20}N_1P_1S_1O_6Na_1$ *m/z* (M+Na) 372.1 (100%); Chiral HPLC using a WHELK O-2 column eluting with 10:120:40 2-propanol–hexanes–1,2-dichloroethane at 1 mL/min afforded the contaminating (*R*)-enantiomer (t_R = 22.7 min) as a very small unresolved shoulder superimposed on the (*S*)-enantiomer (t_R = 25.02 min).

4.4. General procedure for reaction of sulfamidates 1 and 2 with sodium cyanide

4.4.1. Diethyl (2*R*)-cyano-{*N*-benzylamino}methylphosphonate 9a. To a solution of the (*R*)-sulfamidate **1** (0.050 g, 0.1428 mmol) in 0.5 mL of dry DMF under N_2 was added solid NaCN (0.008 g, 0.1570 mmol) (*Caution*: conduct reaction in a fume hood). The mixture was stirred overnight followed by removal of the DMF in vacuo.

4.4.1.1. *N*-Sulfate removal using the boron trifluoride etherate and *n*-propylthiol procedure. To the residue under N_2 was added 1 mL of dry CH_2Cl_2 and the mixture cooled to 0 °C. To this suspension was added by a microliter syringe boron trifluoride etherate (73 μL, 0.5712 mmol) followed by 30 min of stirring. *n*-Propylthiol (52 μL, 0.5712 mmol) was then added, the cooling bath removed and the mixture stirred for 2 h. At this time concd NH_4OH (2 mL) was added and the mixture

transferred to a separatory funnel with the aid of 5 mL water and 15 mL of CH_2Cl_2. The aqueous phase was extracted with 15 mL of CH_2Cl_2 followed by drying of the pooled organic phases, filtering, and evaporation in vacuo to afford 21.2 mg of an oil. This oil was purified by silica TLC eluting with 1:20 MeOH–$CHCl_3$ to afford 12.6 mg (30% yield) of **9a** as an oil.

4.4.1.2. *N*-Sulfate removal using the boron trifluoride etherate and *N*-hydroxysuccinimide procedure. This procedure is exactly as described previously for *n*-propylthiol except *N*-hydroxysuccinimide (0.066 g, 0.5712 mmol) is substituted for *n*-propylthiol. This afforded 29.5 mg of crude product and following silica TLC 21.6 mg (51% yield) of **9a** was obtained.

4.4.1.3. Characterization data for 9a. $[\alpha]_D^{20} = -11.2$ (*c* 0.760, $CHCl_3$); IR (TF) 3320, 3040, 2995, 2960, 2260, 1470, 1260, 1050, 980, 760, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.36 (t, $J = 7.1$ Hz, 6H, CH_3), 2.01 (br s, 1H, NH), 2.64–2.74 (m, 1H, diastereotopic CH_2CN), 2.76–2.86 (m, 1H, diastereotopic CH_2CN), 3.15–3.23 (m, 1H, CHP), 4.01 (q, 2H, $J = 15.2$ and 15.9 Hz, benzylic CH_2), 4.13–4.27 (m, 4H, $POCH_2$), 7.26–7.40 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.46 (d, $J_{CCOP} = 5.6$ Hz, CH_3CH_2OP), 19.75 (d, $J_{NCCCP} = 4.3$ Hz, CH_2CN), 50.19 (d, $J_{CP} = 155.2$ Hz, CHP), 51.76 (d, $J_{CNCP} = 7.3$ Hz, benzylic), 63.02 (d, $J_{COP} = 7.0$ Hz, CH_3CH_2OP), 117.06 (d, $J_{NCCCP} = 12.4$ Hz, CN), 127.65, 128.50, 128.57, 138.06; ^{31}P NMR ($CDCl_3$): δ 23.72. Positive ion ESMS: calculated: $C_{14}H_{21}N_2P_1O_3Na_1$ *m/z* (M+Na) 319.1. Found: $C_{14}H_{21}N_2P_1O_3Na_1$ *m/z* (M+Na) 319.1 (100%).

4.4.1.4. Characterization data for diethyl (2*S*)-cyano-{*N*-benzylamino}methylphosphonate 10a. Yield 77%; $[\alpha]_D^{20} = +10.2$ (*c* 0.760, $CHCl_3$); IR (TF) 3320, 3040, 2995, 2960, 2275, 1465, 1255, 1050, 980, 750, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.36 (t, $J = 7.1$ Hz, 6H, CH_3), 2.02 (br s, 1H, NH), 2.64–2.72 (m, 1H, diastereotopic CH_2CN), 2.76–2.85 (m, 1H, diastereotopic CH_2CN), 3.14–3.23 (m, 1H, CHP), 4.00 (q, 2H, $J = 13.2$ and 13.6 Hz, benzylic CH_2), 4.13–4.25 (m, 4H, $POCH_2$), 7.24–7.41 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.35 (d, $J_{CCOP} = 5.3$ Hz, CH_3CH_2OP), 19.76 (d, $J_{NCCCP} = 5.1$ Hz, CH_2CN), 50.11 (d, $J_{CP} = 154.9$ Hz, CHP), 51.66 (d, $J_{CNCP} = 7.6$ Hz, benzylic), 62.76 (d, $J_{COP} = 7.0$ Hz, CH_3CH_2OP), 117.10 (d, $J_{NCCCP} = 13.0$ Hz, CN), 127.35, 128.50, 128.21, 138.50; ^{31}P NMR ($CDCl_3$): δ 23.61. Positive ion ESMS: calculated: $C_{14}H_{21}N_2P_1O_3Na_1$ *m/z* (M+Na) 319.1. Found: $C_{14}H_{21}N_2P_1O_3Na_1$ *m/z* (M+Na) 319.0 (100%).

4.5. General method for the 3,5-dinitrobenzoylation of amines for chiral HPLC analysis

4.5.1. Diethyl (2*R*)-cyano-{*N*,*N*-benzyl-3,5-dinitrobenzoyl}methylphosphonate 11. To a solution of the amine **9a** (0.014 g, 0.0466 mmol) in 1.0 mL of CH_2Cl_2 under N_2 was added 3,5-dinitrobenzoyl chloride solid (0.014 g, 0.0583 mmol) followed by Et_3N (8.1 μL, 0.0583 mmol). Silica TLC monitoring after 10 min (EtOAc) showed remaining **9a** so another portion of the acid chloride and Et_3N were added. After 30 min, the mixture was diluted with 10 mL of CH_2Cl_2, transferred to a separatory funnel and washed with 5 mL each of 1 M AcOH, water, saturated aq $NaHCO_3$, and brine. The organic phase was dried, filtered, and evaporated in vacuo to afford 23 mg of residue. This was purified by silica TLC eluting with EtOAc to afford 13.9 mg (61% yield) **11** of an oil. $[\alpha]_D^{20} = -23.0$ (*c* 0.248, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.30–1.45 (m, 6H, CH_3), 2.90–3.04 (m, 1H, diastereotopic CH_2CN), 3.30–3.40 (m, 1H, diastereotopic CH_2CN), 4.00–4.52 (m, 5H, $POCH_2$ and CHP), 4.70 (s, 2H, benzylic CH_2), 7.26–7.45 (m, 5H, aromatic H), 8.60 (br s, 2H, aromatic H), 9.05 (br s, 1H, aromatic H); ^{31}P NMR ($CDCl_3$): δ 19.51. Positive ion ESMS: calculated: $C_{21}H_{24}N_4P_1O_8$ *m/z* (M+H) 491.1 and $C_{21}H_{23}N_4P_1O_8Na_1$ *m/z* (M+Na) 513.1. Found: $C_{21}H_{24}N_4P_1O_8$ *m/z* (M+H) 491.0 (30%) and $C_{21}H_{23}N_4P_1O_8Na_1$ *m/z* (M+Na) 513.1 (100%); Chiral HPLC using a Phenomenex® Chirex *S*-Leu and *R*-NEA 250 × 4.60 mm column eluting with 5% 2-propanol in hexanes at 2 mL/min and monitoring at 254 nm to afford the (*R*)-enantiomer ($t_R = 37.90$ min) and no sign of the (*S*)-enantiomer due to tailing of the other enantiopode.

4.5.2. Characterization data for diethyl (2*S*)-cyano-{*N*,*N*-benzyl-3,5-dinitrobenzoyl}methylphosphonate 12. Yield 51%; $[\alpha]_D^{20} = +21.0$ (*c* 0.280, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.30–1.45 (m, 6H, CH_3), 2.90–3.04 (m, 1H, diastereotopic CH_2CN), 3.30–3.40 (m, 1H, diastereotopic CH_2CN), 4.00–4.52 (m, 5H, $POCH_2$ and CHP), 4.70 (s, 2H, benzylic CH_2), 7.26–7.45 (m, 5H, aromatic H), 8.60 (br s, 2H, aromatic H), 9.05 (br s, 1H, aromatic H); ^{31}P NMR ($CDCl_3$): δ 19.51. Positive ion ESMS: calculated: $C_{21}H_{24}N_4P_1O_8$ *m/z* (M+H) 491.1 and $C_{21}H_{23}N_4P_1O_8Na_1$ *m/z* (M+Na) 513.1. Found: $C_{21}H_{24}N_4P_1O_8$ *m/z* (M+H) 491.0 (50%) and $C_{21}H_{23}N_4P_1O_8Na_1$ *m/z* (M+Na) 513.1 (100%); Chiral HPLC using a Phenomenex® Chirex *S*-Leu and *R*-NEA 250 × 4.60 mm column eluting with 5% 2-propanol in hexanes at 2 mL/min and monitoring at 254 nm to afford the contaminating (*R*)-enantiomer (1.6%, $t_R = 39.02$ min) and the (*S*)-enantiomer (98.4%, $t_R = 41.20$ min) with incomplete baseline separation.

4.6. General procedure for the reaction of 1 and 2 with phenethylamine: use of boron trifluoride etherate and *n*-propylthiol to afford the *N*-sulfates of 9b and 10b

4.6.1. Diethyl (1*R*)-1-{*N*-benzylaminosulfate}-2-[(2-phenylethyl)amino]ethylphosphonate 9b. To a solution of the (*R*)-sulfamidate **1** (0.050 g, 0.1428 mmol) in 0.5 mL of THF under N_2 was added phenethylamine (0.035 g, 0.2856 mmol). The mixture was stirred overnight followed by removal of the THF in vacuo. To the residue under N_2 was added 1.0 mL of CH_2Cl_2, cooled to 0 °C and boron trifluoride etherate (73 μL, 0.5712 mmol) added via microliter syringe. This solution was stirred for 30 min and then *n*-propylthiol (52 μL, 0.5712 mmol) added followed by stirring for 1 h. At this time 1 mL of concd NH_4OH was added, the mixture transferred to a separatory funnel and the aqueous phase extracted with

three 5 mL portions of CH_2Cl_2. The pooled organic phases were washed with brine, dried, filtered, and evaporated in vacuo to afford 97 mg of residue. This residue was purified by preparative silica TLC eluting twice with 1:20 MeOH–$CHCl_3$ containing 0.1% concd NH_4OH. The highest R_f major UV active band was isolated to afford 0.048 g (64% yield) of the *N*-sulfate **9b** as an oil. $[\alpha]_D^{20} = -46.3$ (*c* 0.640, $CHCl_3$); IR (TF) 3460, 3040, 2995, 2965, 1610, 1505, 1460, 1270, 1175, 1035, 975, 760, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.24–1.36 (m, 6H, CH_3), 2.04–2.20 (m, 1H), 2.69–2.75 (m, 2H), 2.82–2.90 (m, 1H), 2.99–3.05 (m, 1H), 3.32–3.37 (m, 1H), 4.10–4.32 (m, 4H, $POCH_2$), 4.62 (d, 1H, $J = 16.1$ Hz, diastereotopic benzylic CH_2), 4.76 (dd, 1H, $J = 11.3$ Hz, CHP), 5.04 (d, 1H, $J = 16.0$ Hz, diastereotopic benzylic CH_2), 7.08–7.20 (m, 2H, aromatic H), 7.21–7.32 (m, 6H, aromatic H), 7.65–7.70 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.33 (d, $J_{CCOP} = 5.1$ Hz, CH_3CH_2OP), 32.13, 46.66 (d, $J_{CCP} = 16.2$ Hz, $PCHCH_2N$), 49.28, 49.92, 52.05 (d, $J_{CP} = 157.0$ Hz, CHP), 62.78 (d, $J = 7.1$ Hz, CH_3CH_2OP), 62.93 (d, $J = 7.0$ Hz, CH_3CH_2OP), 127.14, 127.62, 128.65, 128.75, 129.37, 135.75, 140.04; ^{31}P NMR ($CDCl_3$): δ 19.64. Positive ion ESMS *m/z* range 0–750: calculated: $C_{21}H_{32}N_2P_1O_3$ *m/z* (M−SO_3+H) 391.1 and $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M−SO_3+Na) 413.1. Found: $C_{21}H_{32}N_2P_1O_3$ *m/z* (M−SO_3+H) 391.1 (40%) and $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M−SO_3+Na) 413.1 (100%). Positive ion ESMS *m/z* range 0–2000: calculated: $C_{21}H_{32}N_2P_1O_3$ *m/z* (M−SO_3+H) 391.1, $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M−SO_3+Na) 413.1, $C_{42}H_{62}N_4P_2O_{12}S_2Na_1$ *m/z* (2M+Na) 963.3, $C_{63}H_{93}N_6P_3O_{18}S_3Na_1$ *m/z* (3M+Na) 1433.4, $C_{84}H_{124}N_8P_4O_{24}S_4Na_1$ *m/z* (4M+Na) 1903.6. Found: $C_{21}H_{32}N_2P_1O_3$ *m/z* (M−SO_3+H) 391.1 (8%), $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M−SO_3+Na) 413.1 (20%), $C_{42}H_{62}N_4P_2O_{12}S_2Na_1$ *m/z* (2M+Na) 963.0 (70%), $C_{63}H_{93}N_6P_3O_{18}S_3Na_1$ *m/z* (3M+Na) 1432.9 (100%), $C_{84}H_{124}N_8P_4O_{24}S_4Na_1$ *m/z* (4M+ Na) 1902.7 (60%).

4.6.2. Characterization data for diethyl (1*S*)-1-{*N*-benzylaminosulfate}-2-[(2-phenylethyl)amino]ethylphosphonate 10b. Yield 50%, $[\alpha]_D^{20} = +46.4$ (*c* 0.724, $CHCl_3$); IR (TF) 3460, 3040, 2995, 2965, 1610, 1505, 1460, 1270, 1175, 1035, 975, 760, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30–1.35 (m, 6H, CH_3), 2.15–2.30 (m, 1H), 2.63–2.76 (m, 2H), 2.81–2.90 (m, 1H), 3.00–3.06 (m, 1H), 3.32–3.38 (m, 1H), 4.12–4.31 (m, 4H, $POCH_2$), 4.62 (d, 1H, $J = 16.1$ Hz, diastereotopic benzylic CH_2), 4.77 (dd, 1H, $J = 10.9$ and 11.1 Hz, CHP), 5.04 (d, 1H, $J = 16.1$ Hz, diastereotopic benzylic CH_2), 7.08–7.19 (m, 2H, aromatic H), 7.21–7.31 (m, 6H, aromatic H), 7.67–7.70 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.00–16.36 (m, CH_3CH_2OP), 32.08, 46.61 (d, $J_{CCP} = 17.0$ Hz, $PCHCH_2N$), 49.24, 49.90, 52.00 (d, $J_{CP} = 156.6$ Hz, CHP), 62.76 (d, $J = 7.1$ Hz, CH_3CH_2OP), 63.88 (d, $J = 6.9$ Hz, CH_3CH_2OP), 127.10, 127.57, 128.63, 128.72, 128.96, 135.76, 140.03; ^{31}P NMR ($CDCl_3$): δ 19.70. Positive ion ESMS *m/z* range 0–750: calculated: $C_{21}H_{32}N_2P_1O_3$ *m/z* (M−SO_3+H) 391.1 and $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M−SO_3+Na) 413.1. Found: $C_{21}H_{32}N_2P_1O_3$ *m/z* (M−SO_3+H) 391.0 (100%) and $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M−SO_3+Na) 413.1 (70%).

4.6.3. Synthetic procedure for the synthesis and isolation of the diamines 9c and 10c. The procedure is as described above for **9b** except *N*-hydroxysuccinimide (0.066 g, 0.5712 mmol) was substituted for *n*-propylthiol.

4.6.3.1. Diethyl (1*R*)-1-{*N*-benzylamino}-2-[(2-phenylethyl)amino]ethylphosphonate 9c. Yield 79%; $[\alpha]_D^{20} = -17.7$ (*c* 0.608, $CHCl_3$); IR (TF) 3310, 3045, 2995, 2910, 1601, 1500, 1455, 1400, 1210 (br), 1060, 1035, 970, 790, 750, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27–1.35 (m, 6H, CH_3), 1.93 (br s, 2H, NH), 2.74–2.82 (m, 5H), 2.90–3.07 (m, 2H), 3.84 (d, $J = 13.1$ Hz, 1H, diastereotopic benzylic CH_2), 4.01 (d, $J = 13.1$ Hz, 1H, diastereotopic benzylic CH_2), 4.07–4.20 (m, 4H, CH_3CH_2OP), 7.17–7.33 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.45–16.54 (m, CH_3CH_2OP), 36.26, 48.64 (d, $J_{NCCP} = 5.3$ Hz, NCH_2CHP), 50.60, 52.31 (d, $J_{CNCHP} = 4.2$ Hz, benzylic CH_2), 53.61 (d, $J_{CP} = 148.9$ Hz, CHP), 61.92–62.04 (m, CH_3CH_2OP), 126.08, 127.01, 128.28, 128.36, 128.64, 139.80, 139.89; ^{31}P NMR ($CDCl_3$): δ 27.37. Positive ion ESMS: calculated: $C_{17}H_{22}N_2$ *m/z* (M−$PO(OEt)_2$+H) 253.1, $C_{21}H_{32}N_2P_1O_3$ *m/z* (M+H) 391.1, and $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M+Na) 413.1. Found: $C_{17}H_{22}N_2$ *m/z* (M−$PO(OEt)_2$+H) 253.1 (100%), $C_{21}H_{32}N_2P_1O_3$ *m/z* (M+H) 391.1 (10%), and $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M+Na) 413.1 (10%).

4.6.3.2. Diethyl (1*S*)-1-{*N*-benzylamino}-2-[(2-phenylethyl)amino]ethylphosphonate 10c. Yield 79%; $[\alpha]_D^{20} = +18.5$ (*c* = 0.840, $CHCl_3$); IR (TF) 3310, 3035, 2990, 2910, 1601, 1495, 1455, 1400, 1245, 1060, 1035, 970, 790, 755, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28–1.34 (m, 6H, CH_3), 2.02 (br s, 2H, NH), 2.74–2.82 (m, 5H), 2.90–3.07 (m, 2H), 3.84 (d, $J = 13.1$ Hz, 1H, diastereotopic benzylic CH_2), 4.01 (d, $J = 13.1$ Hz, 1H, diastereotopic benzylic CH_2), 4.07–4.20 (m, 4H, CH_3CH_2OP), 7.17–7.33 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.44–16.53 (m, CH_3CH_2OP), 36.26, 48.65 (d, $J_{NCCP} = 5.3$ Hz, NCH_2CHP), 50.62, 52.31 (d, $J_{CNCHP} = 4.3$ Hz, benzylic CH_2), 53.65 (d, $J_{CP} = 148.9$ Hz, CHP), 61.92–62.03 (m, CH_3CH_2OP), 126.06, 127.00, 128.27, 128.40, 128.64, 139.85, 139.91; ^{31}P NMR ($CDCl_3$): δ 27.45. Positive ion ESMS: calculated: $C_{17}H_{22}N_2$ *m/z* (M−$PO(OEt)_2$+H) 253.1, $C_{21}H_{32}N_2P_1O_3$ *m/z* (M+H) 391.1, and $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M+Na) 413.1. Found: $C_{17}H_{22}N_2$ *m/z* (M−$PO(OEt)_2$+H) 253.1 (100%), $C_{21}H_{32}N_2P_1O_3$ *m/z* (M+H) 391.1 (10%), and $C_{21}H_{31}N_2P_1O_3Na_1$ *m/z* (M+Na) 413.1 (10%).

4.7. General procedure for the reaction of 1 and 2 with imidazole

4.7.1. Diethyl (1*R*)-2-(1*H*-imidazol-1-yl)-1-{*N*-benzylamino}ethylphosphonate 9d. To a solution of (*R*)-sulfamidate **1** (0.050 g, 0.1428 mmol) in 2.0 mL of THF under N_2 was added imidazole (0.029 g, 0.4284 mmol). The mixture was stirred for 52 h followed by removal of the THF in vacuo. To the residue under N_2 was added 1.0 mL of CH_2Cl_2, it was cooled to 0 °C and boron trifluoride etherate (73 μL, 0.5712 mmol) added via microliter syringe. *n*-Propylthiol (52 μL, 0.5712 mmol) was then added, the cooling bath was removed and the

mixture stirred for 2 h. At this time 1 mL of concd NH_4OH was added, the mixture transferred to a separatory funnel, and the aqueous phase extracted with three 5 mL portions of CH_2Cl_2. The pooled organic phases were washed with brine, dried, filtered, and evaporated in vacuo to afford 24.1 mg of the residue. This residue was purified by silica TLC eluting with 1:10 MeOH–$CHCl_3$ containing 0.1% concd NH_4OH. The R_f 0.53 UV active band was isolated to afford 0.012 g (23% yield) of **9d** as an oil. $[\alpha]_D^{20} = -26.0$ (*c* 0.238, $CHCl_3$); IR (TF) 3160, 3040, 2995, 2965, 1570, 1470, 1410, 1390, 1250, 1140, 1040, 990, 915, 820, 770, 720 cm^{-1}; ^1H NMR (d_6-DMSO): δ 1.26 (t, $J = 7.0$ Hz, 6H, CH_3), 2.03–2.08 (m, 1H, NH), 3.28–3.39 (m, 1H, CHP), 3.62–3.68 (m, 1H, diastereotopic benzylic CH_2), 3.77–3.85 (m, 1H, diastereotopic benzylic CH_2), 4.00–4.13 (m, 4H, CH_3CH_2OP), 4.17–4.24 (m, 1H), 4.37–4.45 (m, 1H), 6.94–7.16 (m, 5H, aromatic H), 7.48 (s, 1H, imidazoyl), 7.61 (d, $J = 19.8$ Hz, 1H, imidazoyl), 8.73 (d, $J = 18.2$ Hz, 1H, imidazoyl); ^{13}C NMR (d_6-DMSO): δ 16.34–16.38 (m, CH_3CH_2OP), 47.80–48.04 (m), 50.70–50.80 (m), 53.69 (dd, $J_{CP} = 145.6$ and 158.3 Hz, CHP), 61.80–62.10 (m, CH_3CH_2OP), 121.27, 122.21, 122.54, 126.80, 126.83, 127.48, 127.77, 128.16, 136.70, 137.06, 139.90, 139.92; ^{31}P NMR (d_6-DMSO): δ 24.01, 24.08. Positive ion ESMS: calculated: $C_{16}H_{24}N_3P_1O_3$ *m/z* (M+H) 338.1. Found: $C_{16}H_{24}N_3P_1O_3$ *m/z* (M+H) 338.0 (100%). NMR spectra in $CDCl_3$ were broad and complex. Using the *N*-hydroxysuccinimide and boron trifluoride etherate method of *N*-sulfate removal afforded 38% yield of **9d**.

4.7.2. Characterization data for diethyl (1*S*)-2-(1*H*-imidazol-1-yl)-1-{*N*-benzylamino}ethylphosphonate 10d. Yield 25%; $[\alpha]_D^{20} = +26.0$ (*c* 0.266, $CHCl_3$); IR (TF) 3160, 3040, 2990, 2960, 1570, 1470, 1410, 1390, 1250, 1150, 1040, 980, 910, 810, 770, 725 cm^{-1}; ^1H NMR (d_6-DMSO): δ 1.26 (t, $J = 7.0$ Hz, 6H, CH_3), 2.03–2.08 (m, 1H, NH), 3.28–3.39 (m obscured by water, 1H, CHP), 3.62–3.68 (m, 1H, diastereotopic benzylic CH_2), 3.77–3.85 (m, 1H, diastereotopic benzylic CH_2), 4.00–4.13 (m, 4H, CH_3CH_2OP), 4.17–4.24 (m, 1H), 4.37–4.45 (m, 1H), 6.94–7.16 (m, 5H, aromatic H), 7.48 (s, 1H, imidazoyl), 7.61 (d, $J = 19.8$ Hz, 1H, imidazoyl), 8.73 (d, $J = 18.2$ Hz, 1H, imidazoyl); ^{13}C NMR (d_6-DMSO): δ 16.34–16.38 (m, CH_3CH_2OP), 47.80–48.04 (m), 50.70–50.80 (m), 53.69 (dd, $J_{CP} = 145.6$ and 158.3 Hz, CHP), 61.80–62.10 (m, CH_3CH_2OP), 121.28, 122.08, 122.54, 126.80, 126.82, 127.70, 127.78, 128.15, 136.80, 137.06, 139.89, 139.93; ^{31}P NMR (d_6-DMSO): δ 24.11, 24.15. Positive ion ESMS: calculated: $C_{16}H_{25}N_3P_1O_3$ *m/z* (M+H) 338.1 and $C_{16}H_{24}N_3P_1O_3Na_1$ *m/z* (M+Na) 360.1. Found: $C_{16}H_{25}N_3P_1O_3$ *m/z* (M+H) 338.0 (100%) and $C_{16}H_{24}N_3P_1O_3Na_1$ *m/z* (M+Na) 360.1 (10%).

4.8. General procedure for the reaction of 1 and 2 with *N*-hydroxysuccinimide

4.8.1. Diethyl 1-[(2*R*)-(2-*N*-benzylamino)-2-(oxophosphino)ethoxy]pyrrolidine-2,5-dione 9e. To a solution of the (*R*)-sulfamidate **1** (0.050 g, 0.1428 mmol) in 0.5 mL of CH_3CN under N_2 was added *N*-hydroxysuccinimide (0.049 g, 0.4284 mmol) and Et_3N (60 μl, 0.4284 mmol). The mixture was stirred for 22 h followed by removal of the THF in vacuo. To the residue under N_2 was added 1.0 mL of CH_2Cl_2. It was then cooled to 0 °C and boron trifluoride etherate (73 μL, 0.5712 mmol) added via microliter syringe. *n*-Propylthiol (52 μL, 0.5712 mmol) was then added, the cooling bath removed, and the mixture stirred for 1 h. At this time 1 mL of concd NH_4OH was added, the mixture transferred to a separatory funnel and the aqueous phase extracted with three 5 mL portions of CH_2Cl_2. The pooled organic phases were washed with brine, dried, filtered, and evaporated in vacuo to afford 57.2 mg. This residue was purified by preparative silica TLC eluting with 1:10 MeOH–$CHCl_3$. The UV active band was isolated to afford 0.040 g (72% yield) of **9e** as an oil. $[\alpha]_D^{20} = -6.6$ (*c* 0.802, $CHCl_3$); IR (TF) 3320, 3040, 2995, 2960, 1790, 1730, 1501, 1459, 1395, 1375, 1250, 1210, 1170, 1050, 970, 840, 795, 750, 705, 655 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (t, $J = 7.1$ Hz, 6H, CH_3), 2.68 (s, 4H, $OCCH_2CH_2CO$), 3.29–3.37 (m, 1H, CHP), 3.99–4.08 (m, 2H, benzylic CH_2), 4.12–4.22 (m, 4H, CH_3CH_2OP), 4.25–4.32 (m, 1H, diastereotopic $PCHCH_2ON$), 4.44–4.51 (m, 1H, diastereotopic $PCHCH_2ON$), 7.22–7.41 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.35–16.43 (m, CH_3CH_2OP), 25.34, 53.12 (d, $J_{CNCHP} = 7.5$ Hz, benzylic CH_2), 54.17 (d, $J_{CP} = 157.5$ Hz, CHP), 62.15–62.75 (m, CH_3CH_2OP), 75.84 (d, $J_{CNCHP} = 11.3$ Hz, CH_2CHP), 127.01, 128.02, 128.50, 139.56, 171.03; ^{31}P NMR ($CDCl_3$): δ 22.73. Positive ion ESMS: calculated: $C_{17}H_{26}N_2P_1O_6$ *m/z* (M+H) 385.1 and $C_{17}H_{25}N_2P_1O_6$ Na_1 *m/z* (M+Na) 407.1. Found: $C_{17}H_{26}N_2P_1O_6$ *m/z* (M+H) 385.0 (25%) and $C_{17}H_{25}N_2P_1O_6$ Na_1 *m/z* (M+Na) 407.0 (100%).

4.8.2. Characterization data for diethyl 1-[(2*S*)-(2-*N*-benzylamino)-2-(oxophosphino)ethoxy]pyrrolidine-2,5-dione 10e. Yield 76%; $[\alpha]_D^{20} = +6.5$ (*c* 0.840, $CHCl_3$); IR (TF) 3320, 3040, 2995, 2960, 1790, 1730, 1501, 1459, 1395, 1375, 1250, 1210, 1170, 1050, 970, 820, 795, 750, 705, 655 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (t, $J = 7.1$ Hz, 6H, CH_3), 2.68 (s, 4H, $OCCH_2CH_2CO$), 3.28–3.37 (m, 1H, CHP), 3.99–4.10 (m, 2H, benzylic CH_2), 4.13–4.22 (m, 4H, CH_3CH_2OP), 4.25–4.31 (m, 1H, diastereotopic $PCHCH_2ON$), 4.45–4.52 (m, 1H, diastereotopic $PCHCH_2ON$), 7.22–7.45 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.39 (d, $J = 5.6$ Hz, CH_3CH_2OP), 25.35, 52.15 (d, $J_{CNCHP} = 7.4$ Hz, benzylic CH_2), 54.19 (d, $J_{CP} = 157.7$ Hz, CHP), 62.59–62.76 (m, CH_3CH_2OP), 75.85 (d, $J_{CNCHP} = 7.0$ Hz, CH_2CHP), 126.97, 128.26, 128.51, 139.58, 171.03; ^{31}P NMR ($CDCl_3$): δ 22.73. Positive ion ESMS: calculated: $C_{17}H_{26}N_2P_1O_6$ *m/z* (M+H) 385.1 and $C_{17}H_{25}N_2P_1O_6$ Na_1 *m/z* (M+Na) 407.1. Found: $C_{17}H_{26}N_2P_1O_6$ *m/z* (M+H) 385.0 (25%) and $C_{17}H_{25}N_2P_1O_6$ Na_1 *m/z* (M+Na) 407.0 (100%).

4.9. General procedure for the reaction of 1 and 2 with sodium borohydride

4.9.1. Diethyl (1*R*)-1-{*N*-benzylamino}ethylphosphonate 9f. To a solution of (*R*)-sulfamidate **1** (0.050 g, 0.1428 mmol) in 0.5 mL of THF under N_2 was added

$NaBH_4$ (0.006 g, 0.1570 mmol). The mixture was stirred for 18 h followed by removal of the THF in vacuo. To the residue under N_2 was added 1.0 mL of CH_2Cl_2. It was then cooled to 0 °C and boron trifluoride etherate (73 μL, 0.5712 mmol) added via microliter syringe. *n*-Propylthiol (52 μL, 0.5712 mmol) was then added, the cooling bath removed and the mixture stirred for 1 h. At this time 1 mL of concd NH_4OH was added, the mixture transferred to a separatory funnel and the aqueous phase extracted with three 5 mL portions of CH_2Cl_2. The pooled organic phases were washed with brine, dried, filtered, and evaporated in vacuo to afford 22.1 mg of a residue that appeared pure by NMR. This residue was purified by silica TLC eluting with 1:10 MeOH–$CHCl_3$ containing 0.1% concd NH_4OH. The UV active band was isolated to afford 0.014 g (35% yield) of **9f** as an oil. $[\alpha]_D^{20} = -6.0$ (*c* 0.212, MeOH); IR (TF) 3320, 3040, 2995, 2965, 1510, 1460, 1410, 1380, 1250, 1050, 1040, 970, 810, 750, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30–1.38 (m, 9H, CH_3), 1.95 (br s, 1H, NH), 2.96–3.06 (m, 1H, CHP), 3.90 (d, $J = 13.3$ Hz, 1H, diastereotopic benzylic CH_2), 3.97 (d, $J = 13.5$ Hz, 1H, diastereotopic benzylic CH_2), 4.09–4.21 (m, 4H, CH_3CH_2OP), 7.22–7.37 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 15.06 (CH_3), 16.48–16.58 (m, CH_3CH_2OP), 49.14 (d, $J_{CP} = 154.7$ Hz, CHP), 51.41 (d, $J_{CNCHP} = 10.9$ Hz, benzylic CH_2), 62.00–62.12 (m, CH_3CH_2OP), 127.10, 128.16, 128.49, 139.57; ^{31}P NMR ($CDCl_3$): δ 28.70. Positive ion ESMS: calculated: $C_{13}H_{23}N_1P_1O_3$ *m/z* (M+H) 272.1 and $C_{13}H_{22}N_1P_1O_3Na_1$ *m/z* (M+Na) 294.1. Found: $C_{13}H_{23}N_1P_1O_3$ *m/z* (M+H) 272.0 (40%) and $C_{13}H_{22}N_1P_1O_3Na_1$ *m/z* (M+Na) 294.0 (100%). Using the *N*-hydroxysuccinimide and boron trifluoride etherate method of *N*-sulfate removal afforded 84% yield of **9f**.

4.9.2. Characterization data for diethyl (1*S*)-1-{*N*-benzylamino}ethylphosphonate 10f. Yield 64%; $[\alpha]_D^{20} = +6.2$ (*c* 0.422, MeOH); IR (TF) 3310, 3040, 2995, 2960, 1501, 1465, 1400, 1380, 1245, 1065, 1035, 970, 805, 750, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30–1.37 (m, 9H, CH_3), 1.74 (br s, 1H, NH), 2.96–3.05 (m, 1H, CHP), 3.88 (d, $J = 13.3$ Hz, 1H, diastereotopic benzylic CH_2), 3.96 (d, $J = 13.2$ Hz, 1H, diastereotopic benzylic CH_2), 4.10–4.21 (m, 4H, CH_3CH_2OP), 7.22–7.36 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 15.05 (CH_3), 16.44–16.53 (m, CH_3CH_2OP), 49.06 (d, $J_{CP} = 154.8$ Hz, CHP), 51.38 (d, $J_{CNCHP} = 11.3$ Hz, benzylic CH_2), 61.98–62.13 (m, CH_3CH_2OP), 127.01, 128.11, 128.40, 139.67; ^{31}P NMR ($CDCl_3$): δ 28.50. Positive ion ESMS: calculated: $C_{13}H_{23}N_1P_1O_3$ *m/z* (M+H) 272.1 and $C_{13}H_{22}N_1P_1O_3Na_1$ *m/z* (M+Na) 294.1. Found: $C_{13}H_{23}N_1P_1O_3$ *m/z* (M+H) 272.0 (40%) and $C_{13}H_{22}N_1P_1O_3Na_1$ *m/z* (M+Na) 294.0 (100%).

4.10. General procedure for the reaction of 1 and 2 with thiols using cesium carbonate

4.10.1. Diethyl (1*R*)-2-(propylsulfanyl)-1-{*N*-benzylamino}ethylphosphonate 9g. To a solution of (*R*)-sulfamidate **1** (0.050 g, 0.1428 mmol) in 0.25 mL of DMF under N_2 was added *n*-propylthiol (26 μL, 0.2856 mmol) and cesium carbonate (0.094 g, 0.2856 mmol). The mixture was stirred for 2 h followed by removal of the DMF in vacuo. To the residue under N_2 was added 1.0 mL of CH_2Cl_2. It was then cooled to 0 °C and boron trifluoride etherate (73 μL, 0.5712 mmol) added via microliter syringe. *n*-Propylthiol (52 μL, 0.5712 mmol) was then added, the cooling bath removed and the mixture stirred for 1 h. At this time the mixture was transferred to a separatory funnel with the aid of 15 mL of CH_2Cl_2 and 5 mL of water. The aqueous phase was extracted with three 5 mL portions of CH_2Cl_2. The pooled organic phases were washed with brine, dried, filtered, and evaporated in vacuo to afford 36.0 mg of the residue. The residue was purified by silica TLC eluting with EtOAc. The UV active band (R_f 0.57) was isolated to afford 0.028 g (57% yield) of **9g** as an oil. $[\alpha]_D^{20} = -90.3$ (*c* 0.568, $CHCl_3$); IR (TF) 3330, 3040, 2990, 2970, 1501, 1460, 1400, 1250, 1060, 1030, 965, 800, 745, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.94 (t, 3H, $J = 7.2$ and 7.5 Hz, $SCH_2CH_2CH_3$), 1.32–1.37 (m, 6H, CH_3CH_2OP), 1.47–1.58 (m, 2H, $SCH_2CH_2CH_3$), 2.23–2.36 (m, 2H, $SCH_2CH_2CH_3$), 2.50 (br s, 1H, NH), 2.66–2.75 (m, 1H, CHP), 2.99–3.07 (m, 2H, SCH_2CHP), 3.98 (d, $J = 13.2$ Hz, 1H, diastereotopic benzylic CH_2), 4.10 (d, $J = 13.2$ Hz, 1H, diastereotopic benzylic CH_2), 4.15–4.25 (m, 4H, CH_3CH_2OP), 7.24–7.43 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 13.36 (CH_3), 16.53 (d, $J_{CCOP} = 5.3$ Hz, CH_3CH_2OP), 22.56 ($SCH_2CH_2CH_3$), 32.59 (d, $J_{SCCP} = 2.4$ Hz, SCH_2CHP), 33.84 ($SCH_2CH_2CH_3$), 52.38 (d, $J_{CNCHP} = 3.3$ Hz, benzylic CH_2), 52.72 (d, $J_{CP} = 156.8$ Hz, CHP), 62.30 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 62.57 (d, $J_{COP} = 7.2$ Hz, CH_3CH_2OP), 127.17, 128.34, 128.59, 139.20; ^{31}P NMR ($CDCl_3$): δ 25.55. Positive ion ESMS: calculated: $C_{12}H_{19}N_1S_1$ *m/z* (M−$PO(OEt)_2$+H) 208.2, $C_{16}H_{29}N_1P_1O_3S_1$ *m/z* (M+H) 346.1, $C_{16}H_{28}N_1P_1O_3S_1Na_1$ *m/z* (M+Na) 368.1, and $C_{16}H_{28}N_1P_1O_3S_1K_1$ *m/z* (M+K) 384.2. Found: $C_{12}H_{19}N_1S_1$ *m/z* (M− $PO(OEt)_2$+H) 208.2 (100%), $C_{16}H_{29}N_1P_1O_3S_1$ *m/z* (M+H) 346.1 (40%), $C_{16}H_{28}N_1P_1O_3S_1Na_1$ *m/z* (M+ Na) 368.2 (23%), and $C_{16}H_{28}N_1P_1O_3S_1K_1$ *m/z* (M+K) 384.2 (20%).

4.10.2. Diethyl (1*S*)-2-(propylsulfanyl)-1-{*N*-benzylamino}ethylphosphonate 10g. Yield 71%; $[\alpha]_D^{20} = +84.9$ (*c* 0.708, $CHCl_3$); IR (TF) 3310, 3040, 2985, 2970, 1501, 1460, 1400, 1250, 1055, 1030, 965, 800, 750, 705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.94 (t, 3H, $J = 7.3$ Hz, $SCH_2CH_2CH_3$), 1.32–1.38 (m, 6H, CH_3CH_2OP), 1.47–1.58 (m, 2H, $SCH_2CH_2CH_3$), 2.23–2.36 (m, 2H, $SCH_2CH_2CH_3$), 2.55 (br s, 1H, NH), 2.67–2.76 (m, 1H, CHP), 2.99–3.07 (m, 2H, SCH_2CHP), 3.99 (d, $J = 13.2$ Hz, 1H, diastereotopic benzylic CH_2), 4.10 (d, $J = 13.2$ Hz, 1H, diastereotopic benzylic CH_2), 4.12–4.25 (m, 4H, CH_3CH_2OP), 7.24–7.42 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 13.36 (CH_3), 16.53 (d, $J_{CCOP} = 5.6$ Hz, CH_3CH_2OP), 22.56 ($SCH_2CH_2CH_3$), 32.58 (SCH_2CHP), 33.86 ($SCH_2CH_2CH_3$), 52.35 (d, $J_{CNCHP} = 3.3$ Hz, benzylic CH_2), 52.72 (d, $J_{CP} = 156.4$ Hz, CHP), 62.33 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 62.59 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 127.19, 128.35, 128.61, 139.20; ^{31}P NMR ($CDCl_3$): δ 25.47. Positive ion ESMS: calculated: $C_{12}H_{19}N_1S_1$ *m/z* (M−$PO(OEt)_2$+H) 208.2, $C_{16}H_{29}N_1P_1O_3S_1$ *m/z* (M+H) 346.1,

$C_{16}H_{28}N_1P_1O_3S_1Na_1$ *m/z* (M+Na) 368.1, and $C_{16}H_{28}N_1P_1O_3S_1K_1$ *m/z* (M+K) 384.2. Found: $C_{12}H_{19}N_1S_1$ *m/z* (M−PO(OEt)$_2$+H) 208.2 (100%), $C_{16}H_{29}N_1P_1O_3S_1$ *m/z* (M+H) 346.1 (50%), $C_{16}H_{28}N_1P_1O_3S_1Na_1$ *m/z* (M+Na) 368.2 (33%), and $C_{16}H_{28}N_1P_1O_3S_1K_1$ *m/z* (M+K) 384.2 (50%).

4.10.3. Diethyl (1*R*)-2-(2-naphthalenesulfanyl)-1-{*N*-benzylamino}ethylphosphonate 9h. Yield 79%; $[\alpha]_D^{20} = -81.2$ (*c* 0.894, $CHCl_3$); IR (TF) 3310, 3030, 2995, 2970, 1740, 1601, 1500, 1460, 1400, 1250, 1050, 1030, 970, 820, 750, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 3H, CH_3CH_2OP), 1.35 (t, J = 7.1 Hz, 3H, CH_3CH_2OP), 3.10–3.27 (m, 2H, SCH_2CHP), 3.56–3.63 (m, 1H, CHP), 3.95 (d, J = 13.0 Hz, 1H, diastereotopic benzylic CH_2), 4.08 (d, J = 13.0 Hz, 1H, diastereotopic benzylic CH_2), 4.10–4.25 (m, 4H, CH_3CH_2OP), 7.17–7.50 (m, 8H, aromatic H), 7.70–7.80 (m, 4H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.45–16.54 (m, CH_3CH_2OP), 34.80 (SCH_2CHP), 52.28 (d, J_{CNCHP} = 3.7 Hz, benzylic CH_2), 52.97 (d, J_{CP} = 153.8 Hz, CHP), 62.51 (d, J_{COP} = 7.2 Hz, CH_3CH_2OP), 62.69 (d, J_{COP} = 7.2 Hz, CH_3CH_2OP), 125.93, 126.56, 127.13, 127.28, 127.63, 127.68, 128.21, 128.60, 128.61, 131.94, 132.33, 133.62; ^{31}P NMR ($CDCl_3$): δ 24.58. Positive ion ESMS: calculated: $C_{19}H_{19}N_1S_1$ *m/z* (M−PO(OEt)$_2$+H) 292.2, $C_{23}H_{29}N_1P_1O_3S_1$ *m/z* (M+H) 430.1, $C_{23}H_{28}N_1P_1O_3S_1Na_1$ *m/z* (M+Na) 452.1, and $C_{23}H_{28}N_1P_1O_3S_1K_1$ *m/z* (M+K) 468.2. Found: $C_{19}H_{19}N_1S_1$ *m/z* (M−PO(OEt)$_2$+H) 292.2 (100%), $C_{23}H_{29}N_1P_1O_3S_1$ *m/z* (M+H) 430.1 (40%), $C_{23}H_{28}N_1P_1O_3S_1Na_1$ *m/z* (M+Na) 452.1 (20%), and $C_{23}H_{28}N_1P_1O_3S_1K_1$ *m/z* (M+K) 468.2 (25%).

4.10.4. Diethyl (1*S*)-2-(2-naphthalenesulfanyl)-1-{*N*-benzylamino}ethylphosphonate 10h. Yield 70%; $[\alpha]_D^{20} = +83.6$ (*c* 0.860, $CHCl_3$); IR (TF) 3305, 3030, 2995, 2960, 1740, 1630, 1601, 1510, 1470, 1400, 1255, 1050 (br), 975, 830, 760, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (m, 3H, CH_3CH_2OP), 2.42 (br s, 1H, NH), 3.08–3.21 (m, 2H, SCH_2CHP), 3.54–3.62 (m, 1H, CHP), 3.91 (d, J = 13.0 Hz, 1H, diastereotopic benzylic CH_2), 4.04 (d, J = 13.0 Hz, 1H, diastereotopic benzylic CH_2), 4.12–4.24 (m, 4H, CH_3CH_2OP), 7.18–7.50 (m, 8H, aromatic H), 7.68–7.80 (m, 4H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.46–16.52 (m, CH_3CH_2OP), 35.04 (d, J = 4.5 Hz, 2H, SCH_2CHP), 52.44 (d, J_{CNCHP} = 4.5 Hz, benzylic CH_2), 53.18 (d, J_{CP} = 153.0 Hz, CHP), 62.43 (d, J_{COP} = 7.2 Hz, CH_3CH_2OP), 62.58 (d, J_{COP} = 7.3 Hz, CH_3CH_2OP), 125.90, 126.56, 127.11, 127.14, 127.63, 127.68, 128.16, 128.29, 128.44, 128.60, 131.92, 132.46, 133.62; ^{31}P NMR ($CDCl_3$): δ 25.10. Positive ion ESMS: calculated: $C_{19}H_{19}N_1S_1$ *m/z* (M−PO(OEt)$_2$+H) 292.2, $C_{23}H_{29}N_1P_1O_3S_1$ *m/z* (M+H) 430.1. Found: $C_{19}H_{19}N_1S_1$ *m/z* (M−PO(OEt)$_2$+H) 292.2 (85%), $C_{23}H_{29}N_1P_1O_3S_1$ *m/z* (M+H) 430.1 (100%).

4.10.5. Diethyl (1*R*)-1-{*N*-benzylamino}-2-[(2-phenylethyl)acetylamino]ethylphosphonate 13. To a solution of (*R*)-sulfamidate **1** (0.050 g, 0.1428 mmol) in 0.25 mL of THF under N_2 was added phenethylamine (0.035 g, 0.2856 mmol). The mixture was stirred overnight followed by removal of the THF in vacuo. To the residue under N_2 was added 0.5 mL of CH_2Cl_2, Et_3N (20 μL, 0.1428 mmol) followed by acetic anhydride (41 μL, 0.4284 mmol), and then another portion of Et_3N (40 μL, 0.2856 mmol). The reaction mixture was stirred for 1 h, then cooled to 0 °C and boron trifluoride etherate (146 μL, 1.1424 mmol) added via microliter syringe. This solution was stirred for 30 min and then solid *N*-hydroxysuccinimide (0.132 g, 1.1424 mmol) was added followed by stirring for 1 h. At this time 1 mL of concd NH_4OH was added, the mixture transferred to a separatory funnel and the aqueous phase extracted with three 5 mL portions of CH_2Cl_2. The pooled organic phases were washed with brine, dried, filtered, and evaporated in vacuo to afford 84 mg of the residue. This residue was purified by preparative silica TLC eluting with EtOAc to afford (R_f 0.28) 0.043 g (69% yield) of the *N*-acetyl **13** as an oil; $[\alpha]_D^{20} = -33.5$ (*c* 0.860, $CHCl_3$); IR (TF) 3300, 3030, 3015, 2990, 2970, 1650, 1601, 1505, 1465, 1380, 1255, 1175, 1050 (br), 975, 801, 760, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31–1.42 (m, 6H, CH_3), 1.79 and 2.11 (s, 3H, acetyl CH_3 rotomers), 2.69–2.81 (m, 2H), 2.95–3.48 (m, 4H), 3.56–3.71 (m, 1H), 3.79–3.86 (m, 1H, diastereotopic benzylic CH_2), 4.00 (d, 1H, J = 13.5 Hz, diastereotopic benzylic CH_2), 4.08–4.26 (m, 4H, $POCH_2$), 7.08–7.36 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.44–16.54 (m, CH_3CH_2OP), 21.16 and 21.91 (acetyl CH_3), 33.52, 34.74, 45.82, 45.91, 47.64, 49.51, 49.61, 51.17, 51.83, 51.99, 52.50, 52.54, 52.75, 53.32, 53.41, 62.22–62.34 (m, CH_3CH_2OP), 126.19, 126.66, 126.99, 127.35, 128.24, 128.31, 128.38, 128.45, 128.51, 128.64. 128.68, 128.73, 137.95, 139.02, 139.21, 139.87, 170.91, and 171.47 (acetyl carbonyl); ^{31}P NMR ($CDCl_3$): δ 26.06. Positive ion ESMS: calculated: $C_{23}H_{33}N_2P_1O_4$ *m/z* (M+Na) 455.2; Found: $C_{23}H_{33}N_2P_1O_4$ *m/z* (M+Na) 455.2 (100%).

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