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Optically active diethyl *N*-(*p*-toluenesulfonyl)-aziridine 2-phosphonates as chiral synthons for the synthesis of β-substituted α-amino phosphonates

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Abstract—A versatile approach for the synthesis of both protected enantiomers of aziridine 2-phosphonates for use as chiral synthons has been developed. The aziridines arise from either (*R*)- or (*S*)-phosphonoserine diethyl esters followed by *N*-tosylation, *O*-mesylation and cyclization with sodium hydride. These highly enantio-enriched aziridine 2-phosphonates have been shown to react with carbon, nitrogen, sulfur, hydride, fluoride, and phosphorus nucleophiles allowing for the rapid production of a variety of β-substituted α-amino phosphonates in either the (*R*)- or (*S*)-configurations. In the case of thiol nucleophiles, use of a stoichiometric amount of tri-*n*-butylphosphine was necessary to cleanly produce the corresponding sulfide products. Chiral HPLC methods were utilized to monitor the synthetic processes to evaluate the enantiomeric excess of the products obtained when possible.

1. Introduction

The diverse biological activities of α-aminoalkylphosphonic acids and their analogues have stimulated increasing attention among scientists in a wide number of disciplines. The antibacterial, antiviral, anticancer, pesticide, and herbicidal activity of these amino acid structural analogues have been well documented[1–3] and will only continue to expand in the future. Numerous methods[4–25] for the racemic and enantioselective synthesis of this important group of compounds have been undertaken over the last two decades. Recent reports on catalytic asymmetric synthesis[26,27] and the asymmetric synthesis of α-amino thiophosphonates[28] demonstrate the continuing interest in methods that produce a defined configuration α to the phosphorus atom. Despite the many elegant methods for enantioselective synthesis, a need exists for an available chiral synthon to rapidly produce diverse side chain analogues from commercially available nucleophiles especially for combinatorial chemistry libraries. This would avoid the dependence on 'chelation control' for asymmetric induction and for the independent synthesis of each side chain precursor for each unique compound desired. Chiral aziridines with the highly strained three-member ring have been shown to open with both stereo- and regiocontrol to produce chiral amines as recently reviewed.[29–31] Aziridine 2-phosphonates[23,32–38] have been produced by a variety of methods and have shown promise as a flexible electrophile. Due to the activating effect of the *N*-tosyl group of the nitrogen of aziridines such as **1** and **2** (Scheme 1), the potential for nucleophilic attack at the C-3 methylene carbon should provide a smooth route to a structurally diverse class of β-substituted α-amino phosphonates under mild conditions with minimum potential for loss of stereochemical integrity. Herein, we report on our investigations in the use of aziridine-2-phosphonates **1** and **2**, derived from either (*R*)- or (*S*)-phosphonoserine, and their reactions with commercially available heteroatoms and other select nucleophiles.

2. Results and discussion

2.1. Synthesis of aziridine 2-phosphonates 1 and 2

Success and further application of this approach for combinatorial approaches relies on the production of large amounts of both (*R*)- and (*S*)-phosphonoserine in high enantiomeric excess. To achieve this goal, we have chosen the elegant method of Smith[39,40] involving

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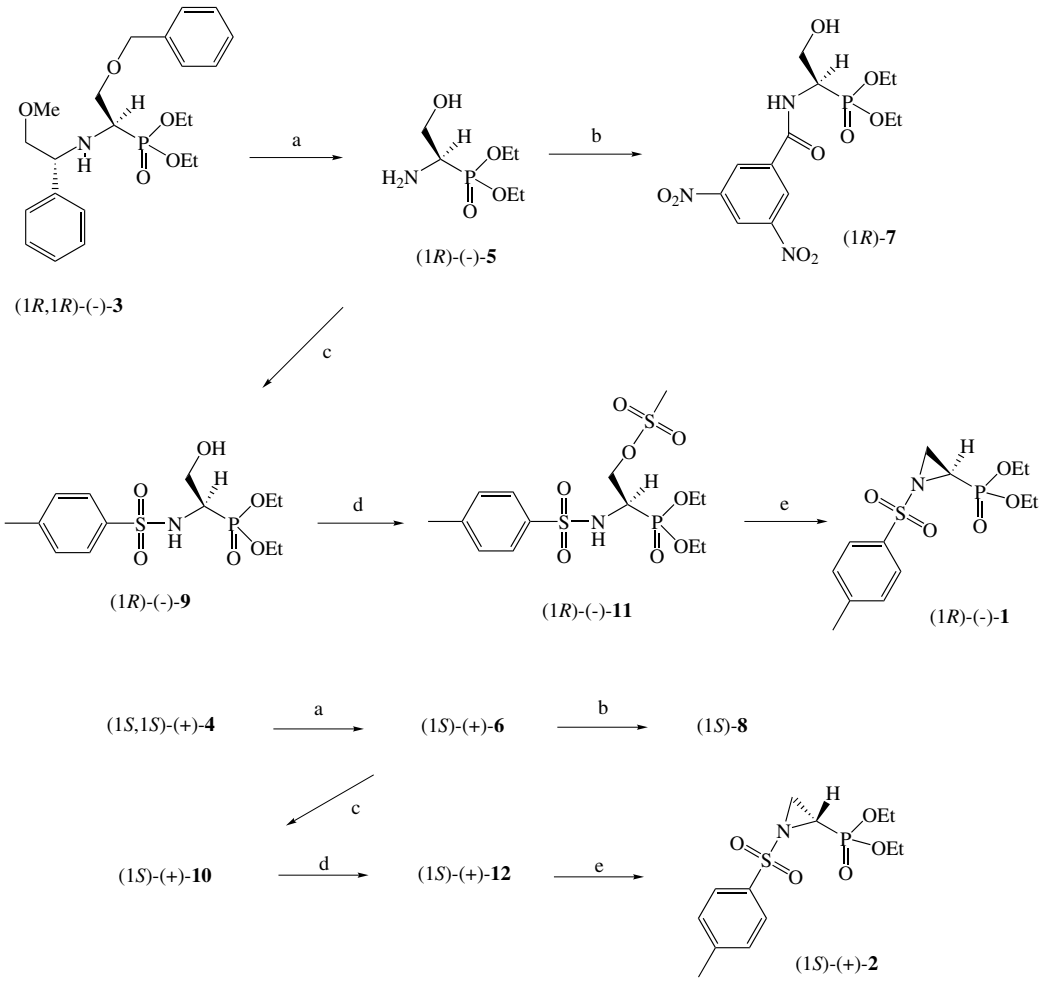


Scheme 1. Syntheses of (1*R*)-(−)-**1** and (1*S*)-(+)-**2** aziridine phosphonates. Reagents and conditions: (a) 20% $Pd(OH)_2/C$, 50 psi H_2, EtOH; (b) 3,5-dinitrobenzoyl chloride, Et_3N, CH_2Cl_2; (c) TsCl, Et_3N, CH_2Cl_2; (d) MsCl, Et_3N, CH_2Cl_2; (e) NaH, THF.

the addition of lithium diethylphosphite to the imine derived from (*O*-benzyl)acetaldehyde[41] and the appropriate chiral auxiliary (*O*-methyl)-phenylglycinol.[42,43] This method proved to be very amenable to reaction scale-up (0.250–0.317 mol) producing both **3** and **4** in 72% and 67% yields (Scheme 1), respectively, following flash silica chromatography and providing enantiomeric excesses of >98% as determined by chiral phase HPLC on a Whelk O-2 column. Both enantiomers were carried forward in parallel in order to monitor stereochemical integrity in all further manipulations when feasible using chiral phase HPLC. The *N*- and *O*-benzyl protecting groups were removed from **3** and **4** by hydrogenation in ethanol to afford the phosphonoserine amino alcohols **5** and **6** in 83% and 86% yield, respectively. Each amino alcohol was converted to the 3,5-dinitrobenzoyl amide derivatives **7** and **8** and examined using a (*S*)-Leu and (*R*)-NEA chiral HPLC column[44,45] affording ee values ranging from 97% to 98%. Both of the amino alcohols **5** and **6** were determined to be stable for a minimum of three months without loss of optically integrity when stored at 0 °C as the free amines.

Conversion of each phosphonoserine enantiomer to the *N*-tosylates **9** (74%) and **10** (54%) was achieved by slow addition of a solution of tosylchloride at 0 °C. Although both aziridines **1** and **2** could be produced from an *N*-, *O*-ditosylate cyclization, we chose the *O*-mesylate due to ease of purification prior to base induced cyclization when compared to the ditosylate. Conversion to the *O*-mesylates **11** and **12** was accomplished smoothly in 75% and 71% yield, respectively, following silica gel chromatography. Purification and characterization of **11** and **12** were complicated by the fact that the mesylates are prone to some degree to spontaneous cyclization. Cyclization of **11** and **12** was accomplished using either NaH in THF or Et_3N in CH_2Cl_2. The Et_3N reaction rate was sluggish when compared to the rapid NaH reaction and produced lower yields of 50–60% when compared to 88–90% for NaH. The aziridine 2-phosphonates **1** and **2** were easily purified by flash silica chromatography and were isolated as oils that can be stored at ambient room temperature for up to one year without any sign of degradation as monitored by TLC and NMR analysis. Specific rotations for each enantiomer are practically identical except for the sign $\{[\alpha]_D^{20} = -29.8$ for **1** and +29.6 for **2**$\}$, however, analysis by chiral HPLC using a Whelk O-2 chiral column proved difficult with incomplete baseline separation despite extensive work on solvent optimization. Chiral HPLC analysis of the

various nucleophile derived products derived from these aziridines **1** and **2** demonstrate (vida infra) that significant racemization did not occur during the three synthetic steps from the phosphonoserines **5** and **6**.

2.2. Reaction of aziridine 2-phosphonates 1 and 2 with nucleophiles

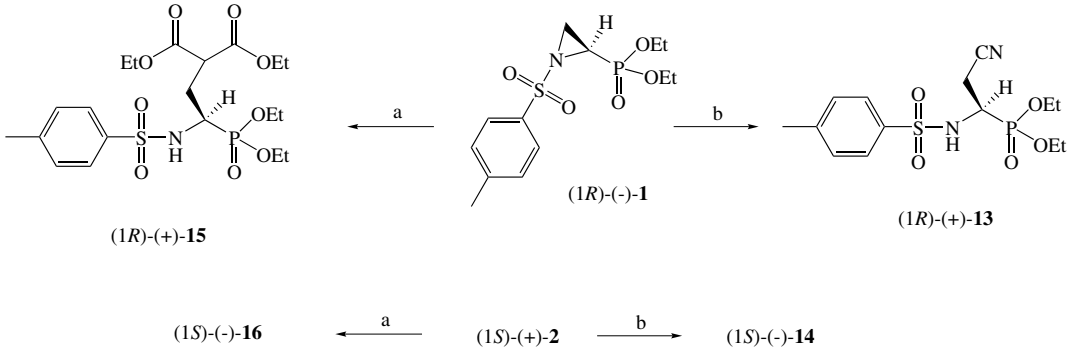
Table 1 summarizes the results of the reactions of enantiomeric aziridine 2-phosphonates with various nucleophiles and includes the specific rotation and HPLC determined % ee values. Scheme 2 describes reactions with the select carbon nucleophiles cyanide and malonate anions. Reaction of aziridines **1** and **2**, with NaCN in DMF afforded cyano adducts **13** and **14** in 87% and 90% yields, respectively. Incomplete separation of the two enantiomers was observed by chiral HPLC making ee determination difficult. Reaction with the anion of diethylmalonate in THF produced **15** and **16** in good yield (81% and 52%, respectively). Analysis of **15** and **16** by Whelk O-2 HPLC revealed no significant loss of enantiomeric excess (98% ee) during the reaction with malonate anion despite specific rotation values differing by 1.1° (+20.8 vs −21.9). These two malonates will prove useful since future elaboration into glutamate, norvaline, pyroglutamate, and proline derivatives are straightforward and will be reported in due course.

Table 1. Addition of select nucleophiles to aziridine 2-phosphonates **1** and **2**

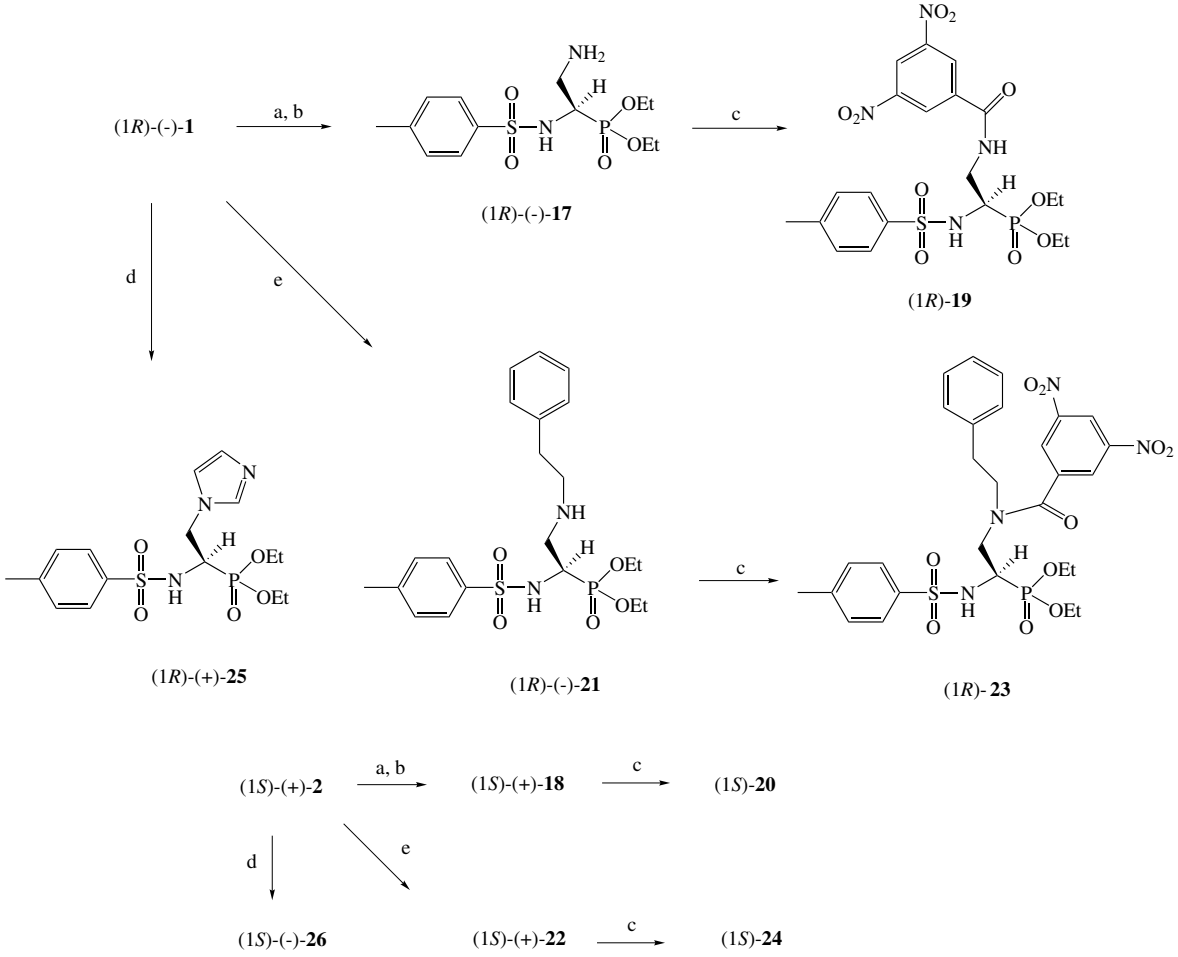
Nucleophile	Entry and configuration	% Yield	$[\alpha]_D^{20}$ [f]	% Ee [a]
—	5*R*	—	−9.1	98[b,d]
—	6*S*	—	+11.7	98[b,d]
—	1*R*	—	−29.8	Incomplete
—	2*S*	—	+29.6	Resolution[c]
NaCN	13*R*	87	+13.5	Incomplete
	14*S*	90	−14.1	Resolution[c]
Sodium malonate	15*R*	81	+20.8	98[c]
	16*S*	52	−21.9	98[c]
NaN_3	17*R*	70	−18.5	98[c,e]
	18*S*	80	+17.0	98[c,e]
Phenethylamine	21*R*	60	+6.8	98[c,d]
	22*S*	71	−6.9	98[c,d]
Imidazole	25*R*	78	+18.5	Inseparable[c]
	26*S*	68	−13.3	
n-Propylthiol	27*R*	36	−19.3	Inseparable[c]
	28*S*	43	+18.0	
Triphenylmethyl	29*R*	46	+1.4	Inseparable[c]
Mercaptan	30*S*	78	−1.4	
$NaBH_4$	32*R*	80	−17.4	98[c]
	33*S*	92	+15.0	98[c]
$(n\text{-Bu})_4NF$	34*R*	53	−11.2	Inseparable[c]
	35*S*	57	+10.2	
Lithium diethyl	36*R*	64	−3.7	Inseparable[c]
Phosphite	37*S*	33	+4.1	

[a] As determined by chiral phase HPLC.
[b] Using a Pirkle (*S*)-Leu and (*R*)-NEA chiral phase column.
[c] Using an (*S*,*S*)-Whelk O-2 chiral phase column.
[d] Following conversion to the 3,5-dinitrobenzoyl derivative.
[e] Following reduction and conversion to the 3,5-dinitrobenzoyl derivative.
[f] Concentration and solvent are listed in Section 4.

Scheme 3 describes the reactions of the nitrogen nucleophiles sodium azide, phenethylamine, and imidazole with the aziridines **1** and **2**. Reactions with sodium azide in DMF followed by hydrogenation of the intermediate alkylazide with 20% $Pd(OH)_2$ on carbon in ethanol afforded primary amines **17** and **18** in 70–80% yields. Phenethylamine in CH_3CN produced secondary amines **21** and **22** in 61–70% yields. The reaction with imidazole was sluggish at room temperature and proved concentration dependent but after extended reaction times, analogues **25** and **26** were isolated in 42–72% yields. Attempts to analyze these β-substituted amines by Whelk O-2 HPLC using a variety of solvents systems failed to produce any sign of enantiomer separation. Derivatization of **17**, **18**, **21**, and **22** as 3,5-dinitrobenzoyl amides **19**, **23**, **20**, and **24** was undertaken, yet examination using an (*S*)-Leu and (*R*)-NEA chiral HPLC column failed to produce any sign of enantiomer resolution. Surprisingly, use of the Whelk O-2 column, which contained a 3,5-dinitrobenzoyl modified solid phase, produced excellent separation. Despite this apparent mismatch of analyte and chiral stationary phase, in which both contained the 3,5-dinitrobenzoyl group, retention time differences on the order of 8–10 min were observed for the enantiomers. In both cases, the enantiomeric excesses observed were 97–98% ee demonstrating again that the starting aziridines **1** and **2** had not been configurationally compromised during the synthetic manipulations from the phosphonoserines **5** and **6** (vida ante).

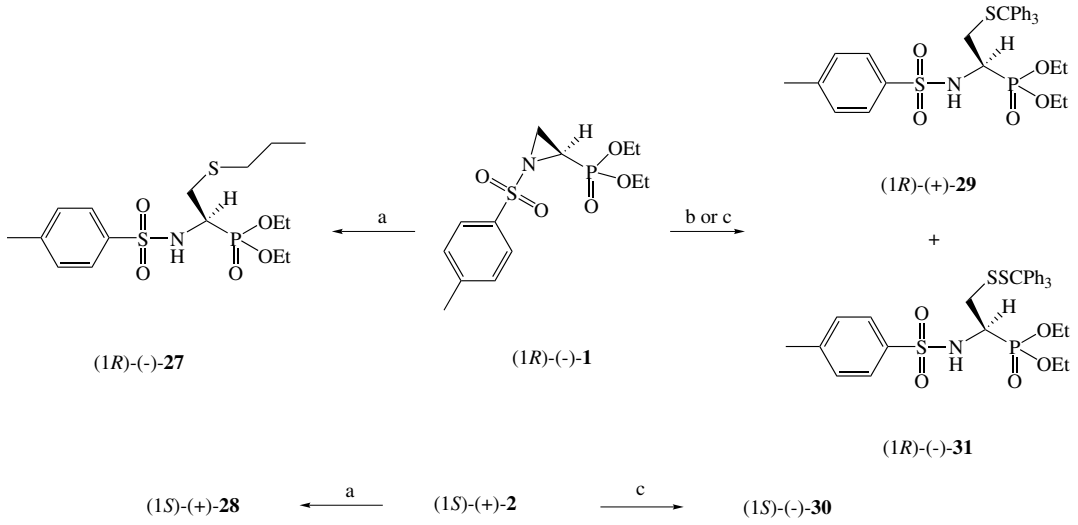


Scheme 2. Select carbon nucleophile reactions with **1** and **2**. Reagents and conditions: (a) NaH, diethylmalonate, THF; (b) NaCN, DMF.

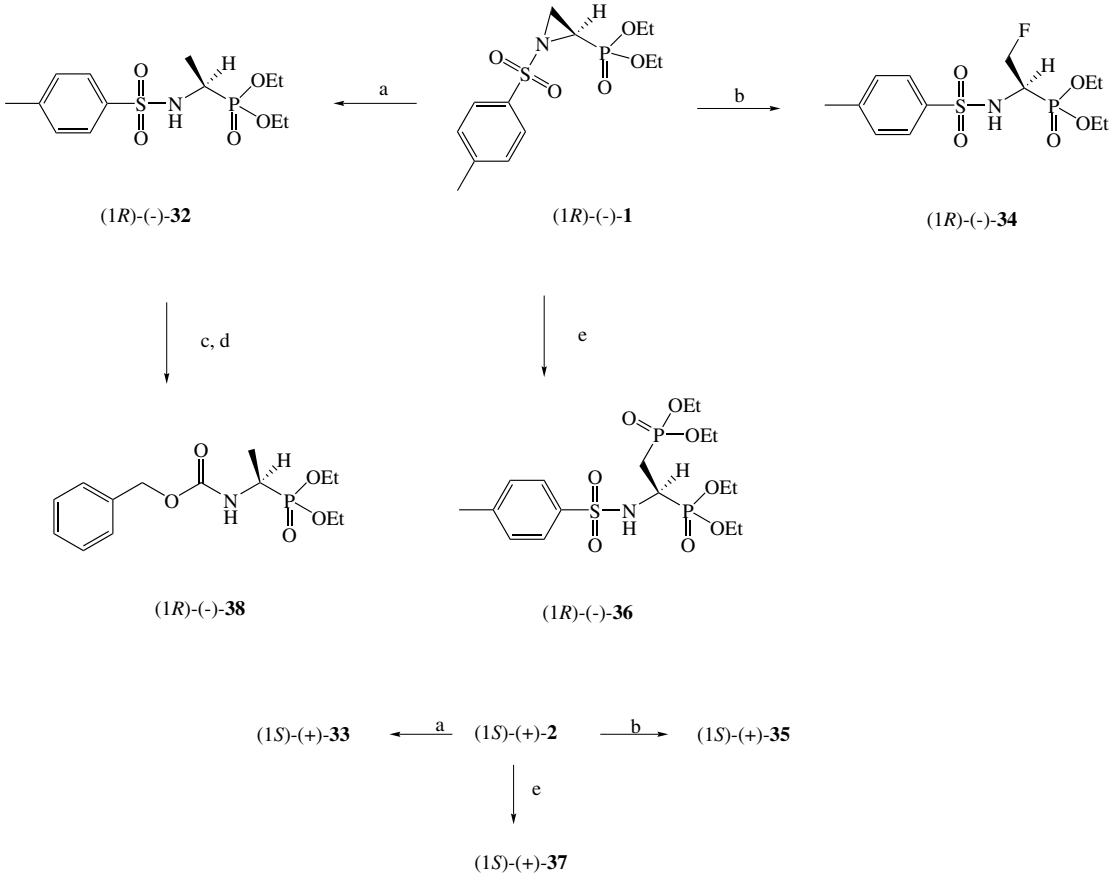


Scheme 3. Select nitrogen nucleophile reactions with **1** and **2**. Reagents and conditions: (a) NaN_3, DMF; (b) 20% $Pd(OH)_2/C$, H_2, EtOH; (c) 3,5-dinitrobenzoyl chloride, Et_3N, CH_2Cl_2; (d) imidazole, CH_3CN; (e) phenethylamine, CH_3CN.

Initially, reaction with simple thiols proved problematic. Scheme 4 shows the reactions of **1** and **2** with the selected thiols *n*-propylthiol and triphenylmethylmercaptan. Treatment of **1** with *n*-propylthiol in the presence of triethylamine produced no trace of desired product **27** and only decomposition of the starting aziridine. Reaction of aziridine **1** with the sodium anion of triphenylmethylmercaptan in THF afforded the desired



Scheme 4. Select thiol nucleophile reactions with **1** and **2**. Reagents and conditions: (a) *n*-Bu_3P, CH_3CN, *n*-PrSH; (b) NaH, THF, $HSCPh_3$; (c) *n*Bu_3P, CH_3CN, $HSCPh_3$.



Scheme 5. Other nucleophile reactions with **1** and **2**. Reagents and conditions: (a) $NaBH_4$, THF; (b) TBAF, THF; (c) Na/NH_3, EtOH, THF, −78 °C; (d) Cbz-Cl, $NaHCO_3$, THF, H_2O; (e) *n*-BuLi, $HPO(OEt)_2$, THF.

sulfide product **29** (36%), recovered aziridine **1** (26%) and the interesting disulfide **31** (5%). This unusual disulfide product was very difficult to remove by silica chromatography and its identity was confirmed spectroscopically and by ESI-MS. Inclusion of 1.0 equiv of tri-*n*-butylphosphine[46] in the reaction and a slight excess of thiol in the complete absence of any additional base suppressed the formation of the disulfide and afforded the analogues **29** and **30** in the 60–80% yield range on a 0.1426 mmol scale. Scale-up production of **29** to a 8.102 mmol scale afforded a 46% yield following flash silica gel chromatography with complete absence of disulfide **31**. Reaction of **1** and **2** with *n*-propylthiol and tri-*n*-butylphosphine afforded sulfides **27** and **28** in 36% and 43% yields, respectively. Boron trifluoride etherate in an equimolar amount and in the presence of excess *n*-propylthiol (as the solvent) at reflux did afford **27** and **28** but was an undesirable approach since not all thiols can be used as a reflux solvent. Use of a catalytic amount of tri-*n*-butylphosphine as reported by Hou et al.[46] in the reaction with aziridines **1** and **2** produced only trace amounts of products as monitored by silica TLC.

Reactions of **1** and **2** with several other commercial nucleophiles of interest are shown in Scheme 5. Reduction by $NaBH_4$ in THF conveniently afforded near quantitative yields of the protected phosphonoalanines **32** and **33** with no evidence of racemization. Removal of the *N*-tosyl group was accomplished using dissolving metal (Na in NH_3) reduction followed by *N*-protection with Cbz-Cl to afford **38** in 68% yield. Attempts at removal[47] of the *N*-tosylate group using Mg metal in methanol/ultrasound or with sodium naphthalide were unsuccessful. Despite these difficulties, this established that dissolving metal (Na) mediated deprotection could be utilized for *N*-tosyl group removal without extensive loss of enantiomeric excess. Attempts at chiral HPLC of *N*-tosylate **32** failed, however once replaced with the *N*-Cbz group successful separation occurred (90% ee). Reaction of the enantiomeric aziridines with tetrabutylammonium fluoride in THF[48] smoothly produced the β-substituted monofluoro analogues **34** and **35** in 53% and 57% yields, respectively, at ambient room temperature. Treatment of **1** and **2** with lithium diethylphosphite in THF afforded the optically active diphosphonates **36** (64%) and **37** (33%). Analysis of the enantiomeric pairs of **34** and **35**, and **36** and **37**, using a Whelk O-2 chiral column failed to produce any sign of enantiomeric resolution under a variety of solvent conditions.

3. Conclusion

In summary, we have demonstrated that aziridine 2-phosphonates **1** and **2** are valuable, stable chiral

synthons for the rapid synthesis of β-substituted α-aminophosphonates. A variety of nucleophiles are capable of reaction and we have observed that the inclusion of tri-*n*-butylphosphine in a stoichiometric amount is necessary for a slight excess of thiol nucleophiles to react successfully. Parallel synthesis and the use of both enantiomers demonstrate that separation of nucleophile derived products by chiral HPLC is not always successful nor predictable. Successful resolution by chiral HPLC further reinforces the notion that the specific rotation can often afford misleading conclusions with respect to absolute enantiopurity. We have observed an apparent mismatch of 3,5-dinitrobenzoyl derivatized analyte and chiral Whelk O-2 column that successfully produced excellent resolution of optical isomers when a matched (*S*)-Leu and (*R*)-NEA chiral HPLC column failed to resolve the enantiomers. Evaluation of these important synthons is currently underway to investigate their reactions with nucleophiles such as cuprates and their potential use in the rapid production of libraries of *S*- and *N*-β-substituted α-amino phosphonates.

4. Experimental

4.1. General

The solvent THF was distilled from sodium benzophenone. Toluene, Et_3N, and CH_2Cl_2 were distilled from CaH_2. DMF was vacuum distilled from CaH_2. Absolute ethanol and $CHCl_3$ were commercial grade and used as purchased. EtOAc and hexanes were distilled prior to use. *n*-Butyllithium was titrated prior to use using 2,3-dimethoxybenzyl alcohol in THF. 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 either a Phenomenex® Chirex (*S*)-Leu and (*R*)-NEA 250 × 4.60 mm column or a Regis (*S*,*S*) Whelk O-2 250 × 4.60 mm column with monitoring at 254 nm. Normal silica phase HPLC was carried out using an Alltech Adsorbosphere SI 5 μm-250 × 4.6 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, ^{31}P, and ^{19}F NMR spectra were obtained using a Bruker Avance 400 MHz NMR and 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. ^{19}F NMR was subject to external reference using hexafluorobenzene at 164.9 ppm and ^{31}P NMR using H_3PO_4 at 0.00 ppm. Specific rotations were obtained in spectral grade solvents. Infrared spectra were obtained as thin films on NaCl plates. Electrospray mass spectra were obtained using a mixture of 1:1 acetonitrile/water containing 0.1% trifluoroacetic acid.

4.1.1. Diethyl (2*R*)-1-[(4-methylphenyl)sulfonyl]aziridin-2-ylphosphonate 1. To a solution of (2*R*)-2-(diethoxyphosphoryl)-2-{[(4-methylphenyl)sulfonyl]amino}ethylmethanesulfonate **11** (4.17 g, 9.70 mmol) in 100 mL of THF at 0 °C was added 60% NaH (0.39 g, 9.70 mmol). The ice bath was removed and the reaction stirred for 3 h at which time TLC (2:1 EtOAc/hexanes) revealed an absence of any starting material. The THF was removed in vacuo and the residue transferred to a separatory funnel using 100 mL of EtOAc. This was washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine. Both aqueous layers were back extracted with two 50 mL portions of EtOAc. The pooled organic phases were dried, filtered, and evaporated in vacuo to afford 3.51 g of a crude oil. The oil was purified by gravity silica gel chromatography (300 mL silica gel) eluting with 2:1 EtOAc/hexanes collecting 20 mL fractions. Homogenous fractions were pooled and evaporated in vacuo to afford 2.86 g (88% yield) of **1** as an oil. $[\alpha]_D^{20} = -29.8$ (*c* 1.00, $CHCl_3$); IR (TF) 3040, 2965, 1604, 1460, 1405, 1340, 1270, 1175, 1035, 920, 830, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, $J = 7.0$ Hz, CH_3), 1.29 (t, 3H, $J = 7.0$ Hz, CH_3), 2.46 (s, 3H, CH_3), 2.51(dd, 1H, $J = 4.6$ and 9.1 Hz, diastereotopic CH_2), 2.74 (dd, 1H, $J = 7.7$ and 9.1 Hz, diastereotopic CH_2), 2.81–2.89 (m, 1H, C*H*P), 3.94–4.14 (m, 4H, POCH_2), 7.36 (d, 2H, $J = 8.3$ Hz, aromatic H), 7.84 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.19 (t, $J_{CCOP} = 5.6$ Hz, CH_3CH_2OP), 21.58, 30.20, 31.25 (d, $J_{CP} = 202$ Hz,), 62.81 (d, $J_{COP} = 6.3$ Hz, CH_3CH_2OP), 63.46 (d, $J_{COP} = 6.3$ Hz, CH_3CH_2OP), 128.26, 129.71, 133.83, 145.16; ^{31}P NMR ($CDCl_3$) δ 16.98; positive ion ESMS: calculated: $C_{13}H_{20}O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 356.1. Found: $C_{13}H_{20}O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 356.1.

4.1.2. Diethyl (2*S*)-1-[(4-methylphenyl)sulfonyl]aziridin-2-ylphosphonate 2. To a solution of (2*S*)-2-(diethoxyphosphoryl)-2-{[(4-methylphenyl)sulfonyl]amino}ethylmethanesulfonate **12** (0.576 g, 1.339 mmol) in 114 mL of THF at 0 °C was added 60% NaH (0.054 g, 1.339 mmol). The ice bath was removed and the reaction stirred for 3 h at which time TLC (2:1 EtOAc/hexanes) revealed an absence of starting material. The THF was removed in vacuo and the residue transferred to a separatory funnel using 50 mL of EtOAc. This was washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine. Both aqueous layers were back extracted with two 50 mL portions of EtOAc. The pooled organic phases were dried, filtered, and evaporated in vacuo to afford 0.500 g of a crude oil. This was purified by gravity silica gel chromatography (50 mL silica gel) eluting with 2:1 EtOAc/hexanes collecting 5 mL fractions. Homogenous fractions were pooled and evaporated in vacuo to afford 0.404 g (90% yield) of **2** as an oil. $[\alpha]_D^{20} = +29.6$ (*c* 0.80, $CHCl_3$); IR (TF) 3040, 2965, 1602, 1450, 1400, 1335, 1260, 1170, 1025, 915, 820, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, $J = 7.1$ Hz, CH_3), 1.29 (t, 3H, $J = 7.1$ Hz, CH_3), 2.46 (s, 3H, CH_3), 2.51 (dd, 1H, $J = 4.6$ and 9.2 Hz, diastereotopic CH_2), 2.74 (dd, 1H, $J = 7.6$ and 9.1 Hz, dia-

stereotopic CH_2), 2.81–2.89 (m, 1H, C*H*P), 3.94–4.14 (m, 4H, POCH_2), 7.36 (d, 2H, $J = 8.3$ Hz, aromatic H), 7.84 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.21 (t, $J_{CCOP} = 5.4$ Hz, CH_3CH_2OP), 21.59, 30.22, 31.27 (d, $J_{CP} = 202$ Hz,), 62.83 (d, $J_{COP} = 6.3$ Hz, CH_3CH_2OP), 63.47 (d, $J_{COP} = 6.3$ Hz, CH_3CH_2OP), 128.27, 129.72, 133.84, 145.17; ^{31}P NMR ($CDCl_3$) δ 16.96; positive ion ESMS: calculated: $C_{13}H_{20}O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 356.1. Found: $C_{13}H_{20}O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 356.1.

4.1.3. Diethyl (1*R*)-(2-*O*-benzyl)-1-{[(1*R*)-2-methoxy-1-phenylethyl]amino}ethyl phosphonate 3.[39,40] To an oven dried, 5 L round bottom flask equipped with mechanical stirrer and 60 mL addition funnel were added 500 g of anhydrous Na_2SO_4, (*R*)-(−)-1-amino-1-phenyl-2-methoxyethane (48.0 g, 0.317 mol) and 950 mL of dry toluene. This mixture was stirred vigorously and cooled to 0 °C using an ice bath. To this cooled suspension was added dropwise over 30 min neat *O*-benzyl-α-hydroxyacetaldehyde (47.5 g, 0.317 mol) followed by removal of the ice bath with stirring continued for 1.5 h. The solid was removed by suction filtration directly into a 3 L round bottom flask using 500 mL of toluene to aid in the process. The toluene was removed in vacuo to afford the crude imine as a pale yellow oil. THF (500 mL) was added and the flask stored under a nitrogen environment.

To an oven dried, 5 L round bottom flask equipped with mechanical stirrer and septa were added diethylphosphite (86.46 g, 0.486 mol) and 1.0 L of THF. This mixture was cooled to 0 °C using an ice bath. A 2.5 M solution of *n*-butyllithium (100 mL, 0.250 mol) was added over 15 min using a stainless steel canula. Stirring was continued for 30 min at 0 °C followed by removal of the ice bath and another 1 h of stirring to ensure complete phosphite anion formation.

The phosphite anion solution was added as fast as possible using a canula to the imine solution at ambient room temperature. THF (50 mL) was used to aid in completing transfer. The reaction mixture was stirred for 12 h followed by the addition of 500 mL of water after which the THF was removed in vacuo. The oil was transferred to a 2 L separatory funnel, 500 mL of water was added, and the mixture extracted with five 500 mL portions of EtOAc. The organic phases were each washed with 250 mL of brine, dried, filtered, and the solvent removed in vacuo to afford 140.4 g of a yellow oil. This oil was purified by flash silica gel chromatography (4 L volume of silica gel) eluting first with 2:1 EtOAc/hexanes and finally with EtOAc to afford 96.0 g (72% yield) of **3** as a clear oil. $[\alpha]_D^{20} = -47.3$ (*c* 0.60, $CHCl_3$); lit.[39,40] $[\alpha]_D^{25} = -49$ (*c* 0.65, $CHCl_3$); IR (TF) 3360, 3010, 1610, 1465, 1400, 1370, 1255, 1040, 970, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, CH_3, $J = 7.1$ Hz), 1.31 (t, 3H, CH_3, $J = 7.1$ Hz), 2.57 (br s, 1H, NH), 2.99–3.05 (m, 1H, C*H*P), 3.36 (s, 3H, OCH_3), 3.39–3.50 (m, 2H, OCH_2), 3.62–3.73 (m, 2H, OCH_2), 4.05–4.20 (m, 4H, POCH_2); 4.38–4.42 (m, 1H, benzylic CH), 4.46 (t, 2H, benzylic CH_2, $J = 12.1$ and 12.9 Hz), 7.22–7.41 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.34 (d, $J_{CCOP} = 6.0$ Hz, CH_3), 16.45 (d, $J_{CCOP} = 5.7$ Hz, CH_3), 52.67 (d, $J_{CP} = 141.7$ Hz,), 58.47, 59.98, 61.80 (t, $J_{COP} = 6.5$ and 6.9 Hz, CH_2OP), 70.47 (d, $J_{CCP} = 3.1$ Hz, CH_2), 73.04, 77.77, 127.38, 127.48, 127.53, 127.90, 128.13, 128.27, 138.03, 140.19; ^{31}P NMR ($CDCl_3$) δ 27.67; positive ion ESMS: calculated: $C_{22}H_{32}O_5N_1P_1$ *m/z* (M + Na) 444.2. Found: $C_{22}H_{32}O_5N_1P_1$ *m/z* (M + Na) 444.2; Silica HPLC 97% pure ($t_R = 14.85$ min) eluting at 1.0 mL/min with 2:1 ethylacetate/hexanes. Chiral HPLC with detection at 254 nm using a Whelk O-2 column eluting at 1.0 mL/min with 80:20:5 hexanes/2-propanol/1,2-dichloroethane to afford a 99:1 ratio of *R*:*S*-enantiomers (*R*-t_R = 10.5 min and *S*-t_R = 8.8 min) or 98% ee.

4.1.4. Diethyl (1*S*)-(2-*O*-benzyl)-1-{[(1*S*)-2-methoxy-1-phenylethyl]amino}ethylphosphonate 4. Diastereomer **4** was synthesized as described above for **3**. The imine was produced from (*S*)-(+)-1-amino-1 phenyl-2-methoxyethane (38.36 g, 0.253 mol) and *O*-benzyl-α-hydroxyacetaldehyde (37.95 g, 0.253 mol). This imine was reacted with the phosphite anion generated from diethylphosphite (69.88 g, 0.506 mol) and 2.53 M *n*-butyllithium (100 mL, 0.253 mol). Work-up was done as described previously with silica gel chromatography affording 71.4 g (67%) of **4** as a clear oil. $[\alpha]_D^{20} = +48.2$ (*c* 0.60, $CHCl_3$); IR (TF) 3360, 3010, 1610, 1465, 1400, 1370, 1255, 1040, 970, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, CH_3, $J = 7.1$ Hz), 1.31 (t, 3H, CH_3, $J = 7.1$ Hz), 2.60 (br s, 1H, NH), 2.96–3.05 (m, 1H, C*H*P), 3.36 (s, 3H, OCH_3), 3.39–3.50 (m, 2H, OCH_2), 3.61–3.75 (m, 2H, OCH_2), 4.00–4.20 (m, 4H, POCH_2); 4.38–4.43 (m, 1H, benzylic CH), 4.47 (t, 2H, benzylic CH_2, $J = 12.0$ and 13.3 Hz), 7.22–7.40 (m, 10 H, aromatic H); ^{13}C NMR ($CDCl_3$) 16.33 (d, $J_{CCOP} = 5.9$ Hz, CH_3), 16.44 (d, $J_{CCOP} = 6.0$ Hz, CH_3), 52.61 (d, $J_{CP} = 141.5$ Hz,), 58.46, 59.93, 61.79 (t, $J_{COP} = 7.2$ and 7.6 Hz, CH_2OP), 70.43 (d, $J_{CCP} = 3.1$ Hz, CH_2), 73.02, 77.74, 127.38, 127.37, 127.48, 127.52, 127.88, 128.15, 128.26, 137.99, 140.14; ^{31}P NMR ($CDCl_3$) δ 27.68; positive ion ESMS: calculated: $C_{22}H_{32}O_5N_1P_1$ *m/z* (M + Na) 444.2. Found: $C_{22}H_{32}O_5N_1P_1$ *m/z* (M + Na) 444.2; Silica HPLC 97% pure ($t_R = 14.85$ min) eluting at 1.0 mL/min with 2:1 ethylacetate/hexanes. Chiral HPLC with detection at 254 nm using a Whelk O-2 column eluting at 1.0 mL/min with 80:20:5 hexanes/2-propanol/1,2-dichloroethane to afford a 0:100 ratio of *R*:*S*-enantiomers (*R*-t_R = undetectable and *S*-t_R = 8.3 min) or >99% ee.

4.2. General method for the hydrogenation of 3 and 4 to afford amino alcohols 5 and 6

4.2.1. Diethyl (1*R*)-1-amino-2-hydroxyethylphosphonate 5.[39,40] A mixture of **3** (10.75 g, 0.025 mol) and 20% $Pd(OH)_2$/C (10.7 g, 60% water by weight) in 100 mL of absolute EtOH was exposed to 50 psi H_2 with shaking for 48 h. The mixture was filtered through a bed of Celite filter aid and the filter pad washed with 100 mL EtOH. The solvents were removed in vacuo to afford 6.47 g of a yellow oil. This was purified by flash silica gel chromatography (250 mL silica gel) eluting with 1:5 EtOH/$CHCl_3$ (containing 0.1% NH_4OH) collecting 50 mL fractions. TLC analysis of the fractions and pooling

produced 4.19 g (83% yield) of **5** as a clear oil. $[\alpha]_D^{20} = -9.1$ (*c* 1.0, $CHCl_3$), lit.[39,40] $[\alpha]_D^{25} = -10.6$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32–1.39 (m, 6H, CH_3), 2.38 (br s, 3H, OH and NH_2), 3.13–3.20 (m, 1H, C*H*P), 3.70–3.90 (m, 2H, HOCH_2), 4.10–4.24 (m, 4H, POCH_2); ^{13}C NMR ($CDCl_3$) δ 16.30–16.40 (m, CH_3), 50.58 (d, $J_{CP} = 146.8$ Hz), 61.88 (d, $J_{CP} = 3.8$ Hz,), 62.16 (d, $J_{COP} = 6.9$ Hz, CH_2OP), 62.31 (d, $J_{COP} = 7.1$ Hz, CH_2OP), ^{31}P NMR ($CDCl_3$) δ 26.94.

4.2.2. Characterization data for diethyl (1*S*)-1-amino-2-hydroxyethylphosphonate 6.[49] 86% yield; $[\alpha]_D^{20} = +11.7$ (*c* 1.0, $CHCl_3$), lit.[49] $[\alpha]_D^{25} = +9.0$ (*c* 1.0, $CHCl_3$); IR (TF) 3320 (br), 2965, 1600, 1450, 1400, 1225, 1050, 975, 800, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 6H, $J = 7.1$ Hz, CH_3), 2.63 (br s, 3H, OH and NH_2), 3.14–3.21 (m, 1H, C*H*P), 3.69–3.77 (m, 1H, HOCH_2), 3.82–3.90 (m, 1H, HOCH_2), 4.09–4.24 (m, 4H, POCH_2); ^{13}C NMR ($CDCl_3$) δ 16.30–16.40 (m, CH_3), 50.57 (d, $J_{CP} = 146.6$ Hz), 61.97 (d, $J_{CP} = 3.8$ Hz,), 62.17 (d, $J_{COP} = 7.0$ Hz, CH_2OP), 62.33 (d, $J_{COP} = 7.0$ Hz, CH_2OP), ^{31}P NMR ($CDCl_3$) δ 26.95.

4.3. General method for 3,5-dinitrobenzoylation of amino alcohols 5 and 6 for chiral HPLC analysis

4.3.1. Diethyl (1*R*)-1-[(3,5-dinitrobenzoyl)amino]-2-hydroxyethylphosphonate 7. A mixture of diethyl (1*R*)-1-amino-2-hydroxyethylphosphonate **5** (20.0 mg, 0.101 mmol) and 3,5-dinitrobenzoyl chloride (29.1 mg, 0.126 mmol) and triethylamine (18 μL, 0.126 mmol) in 1.0 mL of anhydrous CH_2Cl_2 were stirred with TLC monitoring using 1:5 EtOH/$CHCl_3$. After 1 h, no starting amine remained. The reaction mixture was diluted with 10 mL CH_2Cl_2 and washed with 10 mL each of 1 M aqueous AcOH, saturated $NaHCO_3$, and brine. The organic phase was dried, filtered, and evaporated in vacuo to afford 29.3 mg of a white solid. This was applied using CH_2Cl_2 to one glass backed Merck silica gel TLC plate and eluted with 1:20 EtOH/EtOAc. The major UV active band of R_f 0.28 was scraped off and the silica eluted with 1:5 EtOH/$CHCl_3$ to afford the following evaporation in vacuo 18.5 mg (47% yield) of **7** as a white solid. ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H, $J = 7.0$ Hz, CH_3), 1.41 (t, 3H, $J = 7.0$ Hz, CH_3), 3.00–3.80 (br s, 1H, OH), 3.94–4.35 (m, 6H, OCH_2), 4.84–4.92 (m, 1H, C*H*P), 8.83 (d, 1H, $J = 9.5$ Hz, NH), 9.19–9.44 (m, 3H, aromatic H); ^{31}P NMR ($CDCl_3$) δ 22.17; positive ion ESMS: calculated: $C_{13}H_{18}O_9N_3P_1Na_1$ *m/z* (M + Na) 414.1 and $C_{26}H_{36}O_{18}N_6P_2Na_1$ *m/z* (2M + Na) 805.1. Found: $C_{13}H_{18}O_9N_3P_1Na_1$ *m/z* (M + Na) 414.0 and $C_{26}H_{36}O_{18}N_6P_2Na_1$ *m/z* (2M + Na) 804.7; chiral HPLC with detection at 254 nm using a Chirex® column eluting at 1.0 mL/min with 100:100:50:0.25 hexanes/1,2-dichloroethane/2-propanol/trifluoroacetic acid to afford a 98.5:1.5 ratio of *R*:*S*-enantiomers (*R*-$t_R = 25.18$ min and *S*-$t_R = 22.72$ min) or 97% ee.

4.3.2. Characterization data for diethyl (1*S*)-1-[(3,5-dinitrobenzoyl)amino]-2-hydroxyethylphosphonate 8. 52% yield; ^1H NMR (DMSO-d_6) δ 1.18 (t, 3H, $J = 7.0$ Hz, CH_3), 1.24 (t, 3H, $J = 7.0$ Hz, CH_3), 3.95–4.12 (m, 2H, HOCH_2), 4.52–4.65 (m, 1H, C*H*P), 5.08 (t, 1H, $J = 6.5$ Hz, *H*OCH$_2$), 8.95 (t, 1H, $J = 2.5$ and 2.9 Hz, aromatic H), 9.12 (d, 2H, $J = 2.1$ Hz, aromatic H), 9.47 (d, 1H, $J = 9$ Hz, NH); ^{31}P NMR ($CDCl_3$) δ 22.09; positive ion ESMS: calculated: $C_{26}H_{36}O_{18}N_6P_2Na_1$ *m/z* (2M + Na) 805.1. Found: $C_{26}H_{36}O_{18}N_6P_2Na_1$ *m/z* (2M + Na) 804.7; chiral HPLC with detection at 254 nm using a Chirex® column eluting at 1.0 mL/min with 100:100:50:0.25 hexanes/1,2-dichloroethane/2-propanol/trifluoroacetic acid to afford a 7:93 ratio of *R*:*S*-enantiomers (*R*-$t_R = 25.88$ min and *S*-$t_R = 22.17$ min). Accuracy of this determination reflects more (*S*)-enantiomer than actually present due to tailing of the (*R*)-enantiomer making integration of the peak area more difficult.

4.4. General method for *N*-tosylation of amino alcohols 5 and 6

4.4.1. Diethyl (1*R*)-2-hydroxy-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 9. Diethyl (1*R*)-1-amino-2-hydroxyethylphosphonate **5** (8.89 g, 0.0449 mol) in 250 mL of anhydrous CH_2Cl_2 was treated simultaneously by dropwise addition of *p*-toluenesulfonyl chloride (8.56 g, 0.0449 mol) in 100 mL anhydrous CH_2Cl_2 and Et_3N (6.26 mL, 0.0449 mol). The reaction was stirred for 18 h. The mixture was diluted with 250 mL of CH_2Cl_2 and washed with 250 mL portions of 1 M aqueous AcOH, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried, filtered and evaporated to afford 15.95 g of a pale yellow solid. The solid was purified by flash silica gel chromatography (1 L volume of silica gel) eluting first with EtOAc followed by 1:10 EtOH/EtOAc collecting 100 mL fractions. Pure fractions were pooled and evaporated to afford 11.70 g (74% yield) of **9** as a white solid. This solid resisted all attempts at recrystallization. Mp 97–99 °C; $[\alpha]_D^{20} = -11.7$ (*c* 1.00, $CHCl_3$); IR (TF) 3220 (br), 2965, 1602, 1450, 1335, 1230, 1165, 1055, 970, 825, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–1.32 (m, 6H, CH_3), 2.42 (s, 3H, CH_3), 3.43–3.54 (m, 1H), 3.69–3.85 (m superimposed with br s, 3 H), 4.07–4.27 (m, 4H, POCH_2); 6.86 (d, 1H, $J = 9.6$ Hz, NH), 7.29 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.80 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.19–16.35 (m, *C*H$_3$CH$_2$OP), 21.45, 52.74 (d, $J_{CP} = 160.0$ Hz,), 61.43, 63.04 (d, $J_{COP} = 7.0$ Hz, CH$_3$*C*H$_2$OP), 64.06 (d, $J_{COP} = 7.1$ Hz, CH$_3$*C*H$_2$OP), 127.07, 129.63, 138.08, 143.46; ^{31}P NMR ($CDCl_3$) δ 22.53; positive ion ESMS: calculated: $C_{13}H_{22}O_6N_1P_1S_1Na_1$ *m/z* (M + Na) 374.1. Found: $C_{13}H_{22}O_6N_1P_1S_1Na_1$ *m/z* (M + Na) 374.1; Anal Calcd for $C_{13}H_{22}N_1O_6P_1S_1$: C, 44.43; H, 6.32; N, 3.99%. Found: C, 44.68; H, 6.67; N, 3.95%. Silica HPLC 100% pure ($t_R = 6.82$ min) eluting at 1.0 mL/min with 1:10 EtOH/EtOAc. Attempts at chiral HPLC using a Whelk O-2 column were unsuccessful under a variety of conditions.

4.4.2. Characterization data for diethyl (1*S*)-2-hydroxy-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 10. 54% yield; This solid resisted all attempts at recrystallization. Mp 97–99 °C; $[\alpha]_D^{20} = +11.7$ (*c* 1.00, $CHCl_3$); IR (TF) 3200 (br), 2965, 1602, 1450, 1340, 1230, 1165, 1050 (br), 970, 820, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ

1.25–1.31 (m, 6H, CH_3), 2.41 (s, 3H, CH_3), 3.44–3.55 (m, 1H), 3.70–3.79 (m, 2H), 3.92–4.02 (m, 1H), 4.09–4.28 (m, 4H, POCH_2); 7.10 (d, 1H, $J = 9.8$ Hz, NH), 7.30 (d, 2H, $J = 8.0$ Hz, aromatic H), 7.81 (d, 2H, $J = 8.2$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.15–16.31 (m, CH_3CH_2OP), 21.41, 52.84 (d, $J_{CP} = 160.3$ Hz,), 61.38, 63.03 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 64.03 (d, $J_{COP} = 7.0$ Hz, CH_3CH_2OP), 127.00, 129.57, 138.07, 143.36; ^{31}P NMR ($CDCl_3$) δ 22.61; positive ion ESMS: calculated: $C_{13}H_{22}O_6N_1P_1S_1Na_1$ *m/z* (M + Na) 374.1. Found: $C_{13}H_{22}O_6N_1P_1S_1Na_1$ *m/z* (M + Na) 374.1. Attempts at chiral HPLC using a Whelk O-2 column were unsuccessful under a variety of conditions.

4.5. General method for the *O*-mesylation of alcohols 9 and 10

4.5.1. (2*R*)-2-(Diethoxyphosphoryl)-2-{[(4-methylphenyl)sulfonyl]amino}ethylmethanesulfonate 11. To a cooled solution at 0 °C of diethyl (1*R*)-2-hydroxy-1-[(4-methylphenyl)sulfonyl]aminoethylphosphonate **9** (4.70 g, 0.013 mol) in 67 mL of anhydrous CH_2Cl_2 and Et_3N (2.33 mL, 0.017 mol) was added dropwise via syringe methanesulfonyl chloride (1.30 mL, 0.017 mol). The solution was stirred for 15 min followed by removal of the ice bath and stirring for 2 h. The mixture was transferred to a separatory funnel and washed with 100 mL of saturated aqueous $NaHCO_3$ and brine. The organic phase was dried, filtered, and evaporated to afford 6.24 g of an oily semi-solid. This was purified by flash chromatography (600 mL volume silica gel) eluting with EtOAc and collecting 75 mL fractions. Pooled fractions were evaporated in vacuo to afford 4.40 g (77% yield) of **11** as an oil that slowly crystallized. $[\alpha]_D^{20} = -7.1$ (*c* 1.00, benzene); IR (TF) 3200, 3050, 2965, 2880, 1602, 1450, 1340, 1240, 1170, 1030, 970, 820, 720, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 6H, $J = 7.1$ Hz, CH_3), 2.42 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 3.95–4.32 (m, 7H), 6.59 (dd, 1H, $J = 9.4$ and 3.2 Hz, NH), 7.31 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.79 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.18–16.33 (m, CH_3CH_2OP), 21.47, 36.93, 49.81 (d, $J_{CP} = 159.7$ Hz,), 63.24 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 64.30 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 67.58 (d, $J_{CCP} = 6.5$ Hz, CH_2CHP), 127.04, 129.65, 137.79, 143.73; ^{31}P NMR ($CDCl_3$) δ 18.37; positive ion ESMS: calculated: $C_{14}H_{24}O_8N_1P_1S_2Na_1$ *m/z* (M + Na) 352.1. Found: $C_{13}H_{22}O_6N_1P_1S_1Na_1$ *m/z* (M + Na) 352.0.

4.5.2. Characterization data for (2*S*)-2-(diethoxyphosphoryl)-2-{[(4-methylphenyl)sulfonyl]amino}ethylmethanesulfonate 12. 71% yield; $[\alpha]_D^{20} = +9.2$ (*c* 0.972, benzene); IR (TF) 3260, 3120, 2995, 2940, 1602, 1450, 1340, 1245, 1170, 1040, 970, 840, 720, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 6H, $J = 7.1$ Hz, CH_3), 2.42 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 3.94–4.33 (m, 7H), 6.63 (dd, 1H, $J = 9.4$ and 3.2 Hz, NH), 7.31 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.79 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.17–16.38 (m, CH_3CH_2OP), 21.46, 36.89, 49.81 (d, $J_{CP} = 159.8$ Hz,), 63.21 (d, $J_{COP} = 7.2$ Hz, CH_3CH_2OP), 64.30 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 67.57 (d, $J_{CCP} = 6.5$ Hz, CH_2CHP), 127.03, 129.63, 137.80, 143.70; ^{31}P NMR ($CDCl_3$) δ 18.36; positive ion ESMS: calculated: $C_{14}H_{24}O_8N_1P_1S_2Na_1$ *m/z* (M + Na) 452.1. Found: $C_{13}H_{22}O_6N_1P_1S_1Na_1$ *m/z* (M + Na) 452.0.

4.6. General procedure for cyanide addition to aziridines

4.6.1. Diethyl (2*R*)-cyano{[(4-methylphenyl)sulfonyl]amino}methylphosphonate 13. To L-aziridine **1** (3.48 g, 10.43 mmol) in 70 mL DMF was added solid NaCN (0.64 g, 13.038 mmol). The reaction was stirred for 21 h followed by removal of the DMF in vacuo. The residue was diluted with 100 mL of EtOAc and 50 mL of 10% aqueous citric acid (*caution*: work-up must be conducted in a fume hood) and the mixture stirred until all solid material had dissolved. The aqueous phase was extracted with three 100 mL portions of EtOAc and the pooled organic phases washed with brine, dried, filtered, and evaporated in vacuo to afford 3.86 g of an oil. This oil was purified by flash silica gel chromatography (300 mL silica gel) eluting with EtOAc and collecting 20 mL fractions. Pooled homogenous fractions were evaporated in vacuo to afford 3.26 g (87% yield) of **13** as an oil. $[\alpha]_D^{20} = +13.5$ (*c* 2.108, $CHCl_3$); IR (TF) 3100 (br), 2995, 2260, 1601, 1450, 1340, 1240, 1165, 1035, 980, 840, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29–1.34 (m, 6H, CH_3CH_2OP), 2.43 (s, 3H, CH_3), 2.64–2.80 (m, 2H, CH_2CN), 3.84–3.95 (m, 1H, C*H*P), 4.07–4.29 (m, 4H, POCH_2), 6.86 (dd, 1H, $J = 4.5$ and 9.4 Hz, NH), 7.32 (d, 2H, $J = 7.7$ Hz, aromatic H), 7.81 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.14–16.22 (m, CH_3CH_2OP), 19.98 (d, $J_{CCP} = 3.3$ Hz, CH_2CHP), 21.47, 46.33 (d, $J_{CP} = 164$ Hz, *C*HP), 63.45 (d, $J_{COP} = 7.3$ Hz, CH_3CH_2OP), 64.58 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 115.83 (d, $J = 6.8$ Hz, CN), 126.98, 129.77, 137.62, 143.91; ^{31}P NMR ($CDCl_3$) δ 19.11; positive ion ESMS: calculated: $C_{14}H_{21}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 383.1. Found: $C_{14}H_{21}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 383.1. Chiral HPLC using a Whelk O-2 column eluting with 10:120:40 2-propanol/hexanes/1,2-dichloroethane at 1.0 mL/min affords a $t_R = 19.47$ min. Incomplete baseline separation of a 1:1 mixture of enantiomers (L-$t_R = 20.12$ min and D-$t_R = 19.47$ min) occurs when both are injected simultaneously.

4.6.2. Characterization data for diethyl (2*S*)-cyano{[(4-methylphenyl)sulfonyl]amino}methylphosphonate 14. 90% yield; $[\alpha]_D^{20} = -14.1$ (*c* 1.932, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.29–1.34 (m, 6H, CH_3CH_2OP), 2.44 (s, 3H, CH_3), 2.63–2.82 (m, 2H, CH_2CN), 3.80–3.93 (m, 1H, C*H*P), 4.05–4.27 (m, 4H, POCH_2), 6.32 (dd, 1H, $J = 5.1$ and 9.1 Hz, NH), 7.33 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.81 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 19.13; positive ion ESMS: calculated: $C_{14}H_{21}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 383.1. Found: $C_{14}H_{21}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 383.1. Chiral HPLC using a Whelk O-2 column eluting with 10:120:40 2-propanol/hexanes/1,2-dichloroethane at 1.0 mL/min affords a $t_R = 20.12$. Incomplete baseline separation of a 1:1 mixture of enantiomers (L-$t_R = 20.12$ min and D-$t_R = 19.47$ min) occurs when both are injected simultaneously.

4.7. General procedure for malonate anion addition to aziridines

4.7.1. Diethyl [(2*R*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-amino-2-(diethoxyphosphoryl)ethyl]malonate 15. A solution of diethylmalonate (1.33 g, 8.297 mmol) in 40 mL of THF at 0 °C was treated with 60% NaH (0.33 g, 8.297 mmol). The mixture was stirred briskly for 30 min then transferred via canula to a flask containing L-aziridine **1** (2.22 g, 6.637 mmol) in 10 mL of THF followed by a 6 mL THF wash. The reaction was stirred for 60 h at ambient room temperature at which time TLC monitoring (EtOAc) indicated an absence of starting **1**. The THF was evaporated in vacuo, the residue dissolved in 100 mL of EtOAc and washed with 50 mL of brine containing 5 mL of 1 M AcOH. The aqueous phase was extracted with two 50 mL portions of EtOAc, washed with brine, dried, filtered, and evaporated in vacuo to afforded 4.15 g of a crude oil. This was purified by gravity silica column chromatography (400 mL volume silica) eluting with EtOAc and collecting 10 mL fractions. Homogenous fractions were pooled and evaporated in vacuo to afford 2.50 g (76% yield) of malonate **15** as an oil. $[\alpha]_D^{20} = +20.8$ (*c* 0.838, $CHCl_3$); IR (TF) 3120 (br), 2995, 2920, 1740, 1602, 1450, 1345, 1240, 1170, 1030, 980, 825, 675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, 3H, $J = 7.0$ Hz, CH_3CH_2OP), 1.22–1.32 (5, 9H, CH_3CH_2OP and CH_3CH_2OCO), 1.98–2.10 (m, 1H, diastereotopic CH_2), 2.32–2.46 (m, 1H, diastereotopic CH_2), 2.41 (s, 3H, CH_3), 3.77 (dd, 1H, $J = 9.6$ Hz, O_2CCHCO_2), 3.81–4.27 (m, 9H, CHP and CH_3CH_2OP), 5.75 (dd, 1H, $J = 4.7$ and 9.5 Hz, NH), 7.28 (d, 2H, $J = 8.0$ Hz, aromatic H), 7.75 (d, 2H, $J = 8.1$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 13.94 (d, $J_{CCOP} = 5.7$ Hz, CH_3CH_2OP), 16.20, 21.44, 29.75 (d, $J = 6.1$ Hz), 47.84 (d, $J_{CCP} = 12.2$ Hz, CH_2CHP), 48.18 (d, $J_{CP} = 157.7$ Hz, CHP), 61.55, 61.59, 62.78 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 63.03 (d, $J_{COP} = 7.0$ Hz, CH_3CH_2OP), 127.11, 129.41, 137.92, 143.28, 168.7, 169.2; ^{31}P NMR ($CDCl_3$) δ 22.82; positive ion ESMS: calculated: $C_{20}H_{32}O_9N_1P_1S_1Na_1$ *m/z* (M + Na) 516.1. Found: $C_{20}H_{32}O_9N_1P_1S_1Na_1$ *m/z* (M + Na) 516.1. Chiral HPLC using a Whelk O-2 column eluting with 10:120:40 2-propanol/hexanes/1,2-dichloroethane at 1.0 mL/min affords a $t_R = 12.10$ min. Incomplete baseline separation of a 1:1 mixture of enantiomers (L-$t_R = 11.37$ min and D-$t_R = 12.12$ min) occurs when both are injected simultaneously.

4.7.2. Characterization data for diethyl [(2*S*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-amino-2-(diethoxyphosphoryl)ethyl]malonate (16). 52% yield; $[\alpha]_D^{20} = -21.9$ (*c* 1.540, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H, $J = 7.1$ Hz, CH_3CH_2OP), 1.22–1.31 (5, 9H, CH_3CH_2OP and CH_3CH_2OCO), 1.98–2.10 (m, 1H, diastereotopic CH_2), 2.33–2.46 (m, 1H, diastereotopic CH_2), 2.42 (s, 3H, CH_3), 3.74 (dd, 1H, $J = 9.6$ Hz, O_2CCHCO_2), 3.79–4.27 (m, 9H, CHP and CH_3CH_2OP), 5.20 (dd, 1H, $J = 5.5$ and 9.6 Hz, NH), 7.29 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.75 (d, 2H, $J = 8.2$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 22.86; positive ion ESMS: calculated: $C_{20}H_{32}O_9N_1P_1S_1Na_1$ *m/z* (M + Na) 516.1. Found: $C_{20}H_{32}O_9N_1P_1S_1Na_1$ *m/z* (M + Na) 516.1. Chiral HPLC using a Whelk O-2 column eluting with 10:120:40 2-propanol/hexanes/1,2-dichloroethane at 1.0 mL/min affords a $t_R = 11.37$ min. Incomplete baseline separation of a 1:1 mixture of enantiomers (L-$t_R = 11.37$ min and D-$t_R = 12.12$ min) occurs when both are injected simultaneously.

4.8. General method for azide anion addition to aziridines and hydrogenation

4.8.1. Diethyl (1*R*)-2-amino-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 17. To the L-aziridine **1** (50.0 mg, 0.1496 mmol) in 1 mL of DMF was added solid NaN_3 (12.2 mg, 0.1870 mmol). The reaction was stirred for 14 h followed by removal of the DMF in vacuo. The residue was diluted with 2 mL of EtOH, 20% $Pd(OH)_2/C$ (25 mg) then added and the mixture exposed to a balloon of H_2 for 3 h. The catalyst was removed by filtration through a bed of Celite that was washed with 10 mL of EtOH. The solvent was removed in vacuo and the residue purified by thin-layer chromatography eluting with 1:5 MeOH/$CHCl_3$ containing 0.1% NH_4OH. The major UV positive band was removed and eluted with the same solvent to afford 37 mg (70% yield) of **17** as an oil. $[\alpha]_D^{20} = -18.5$ (*c* 0.460, $CHCl_3$); IR (TF) 3120 (br), 2995, 1602, 1450, 1340, 1240, 1170, 1030, 970, 825, 675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–1.30 (m, 6H, CH_3CH_2OP), 2.42 (s, 3H, CH_3), 2.60–2.72 (m, 1H, diastereotopic CH_2N), 2.91–2.98 (m, 1H, diastereotopic CH_2N), 3.10 (br s, 2H, NH_2) 3.59–3.67 (m, 1H, CHP), 4.02–4.20 (m, 4H, $POCH_2$), 7.29 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.79 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.19–16.35 (m, CH_3CH_2OP), 21.43, 41.32 (d, $J_{CCP} = 3.3$ Hz, CH_2CHP), 51.89 (d, $J_{CP} = 157.8$ Hz, CHP), 62.41 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 63.54 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 126.96, 129.58, 138.09, 143.41; ^{31}P NMR ($CDCl_3$) δ 22.45; positive ion ESMS: calculated: $C_{13}H_{24}O_5N_2P_1S_1$ *m/z* (M + H) 351.1 and $C_{13}H_{23}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 373.1. Found: $C_{13}H_{24}O_5N_2P_1S_1Na_1$ *m/z* (M + H) 351.1 and $C_{13}H_{23}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 373.1. Chiral HPLC was conducted after derivatization with 3,5-dinitrobenzoylchloride to afford **19**.

4.8.2. Characterization data for diethyl (1*S*)-2-amino-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 18. 80% yield; $[\alpha]_D^{20} = +17.0$ (*c* 0.154, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26–1.30 (m, 6H, CH_3CH_2OP), 2.42 (s, 3H, CH_3), 2.59–2.72 (m, 1H, diastereotopic CH_2N), 2.94–3.02 (m, 1H, diastereotopic CH_2N), 3.10 (br s, 2H, NH_2), 3.58–3.66 (m, 1H, CHP), 4.01–4.19 (m, 4H, $POCH_2$), 7.30 (d, 2H, $J = 8.3$ Hz, aromatic H), 7.79 (d, 2H, $J = 8.4$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 22.45; positive ion ESMS: calculated: $C_{13}H_{24}O_5N_2P_1S_1Na_1$ *m/z* (M + H) 351.1 and $C_{13}H_{23}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 373.1. Found: $C_{13}H_{24}O_5N_2P_1S_1$ *m/z* (M + H) 351.0 and $C_{13}H_{23}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 373.1. Chiral HPLC was conducted after derivatization with 3,5-dinitrobenzoylchloride to afford **20**.

4.9. General method for addition of phenethylamine to aziridines

4.9.1. Diethyl (1*R*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-[(2-phenylethyl)amino]ethylphosphonate 21. To L-aziridine **1** (50.0 mg, 0.1496 mmol) was added phenethylamine (47 mg, 0.1870 mmol) in 1 mL of CH_3CN. The reaction was stirred for 14 h followed by dilution with 20 mL of *n*-BuOH and 10 mL of water. The aqueous phase was extracted with two 10 mL portions of *n*-BuOH. The solvent was removed in vacuo with the aid of a vacuum pump to afford 90 mg of an oil. The residue was purified by preparative thin-layer chromatography eluting with 1:10 MeOH/$CHCl_3$. The major UV positive band (R_f 0.40) was removed and eluted with the same solvent to afford 63 mg (71% yield) of **21** as an oil. $[\alpha]_D^{20} = -6.9$ (*c* 1.134, $CHCl_3$); IR (TF) 3220 (br), 3035, 2995, 2965, 1602, 1500, 1460, 1340, 1240, 1165, 1025, 975, 820, 705, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23–1.28 (m, 6H, CH_3CH_2OP), 2.26–2.38 (m, 1H, diastereotopic CH_2N), 2.40 (s, 3H, CH_3), 2.48–2.56 (m, 1H, diastereotopic CH_2N), 2.63 (t, 2H, $J = 6.7$ and 7.2 Hz, $ArCH_2$), 2.70–2.77 (m, 1H, diastereotopic CH_2N), 2.89–2.95 (m, 1H, diastereotopic CH_2N), 3.63–3.71 (dq, 1H, CHP), 3.97–4.20 (m, 4H, $POCH_2$), 7.13–7.32 (m, 7H, aromatic H), 7.69 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.16–16.34 (m, CH_3CH_2OP), 21.42, 36.30, 47.67, 49.55 (d, $J_{CP} = 157.8$ Hz, CHP), 50.93, 62.40 (d, $J_{COP} = 7.0$ Hz, CH_3CH_2OP), 63.59 (d, $J_{COP} = 7.2$ Hz, CH_3CH_2OP), 126.09, 126.99, 128.33, 128.57, 129.55, 137.79, 139.82, 143.46; ^{31}P NMR ($CDCl_3$) δ 22.54; positive ion ESMS: calculated: $C_{21}H_{32}O_5N_2P_1S_1$ *m/z* (M + H) 455.2 and $C_{21}H_{31}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 477.2. Found: $C_{21}H_{32}O_5N_2P_1S_1$ *m/z* (M + H) 455.2 and $C_{21}H_{31}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 477.1. Chiral HPLC was conducted after derivatization with 3,5-dinitrobenzoylchloride to afford **23**.

4.9.2. Characterization data for diethyl (1*S*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-[(2-phenylethyl)amino]ethylphosphonate 22. 60% yield; $[\alpha]_D^{20} = +6.8$ (*c* 0.306, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24–1.28 (m, 6H, CH_3CH_2OP), 2.21–2.37 (m, 1H, diastereotopic CH_2N), 2.41 (s, 3H, CH_3), 2.45–2.59 (m, 1H, diastereotopic CH_2N), 2.64 (t, 2H, $J = 6.8$ and 7.1 Hz, $ArCH_2$), 2.72–2.80 (m, 1H, diastereotopic CH_2N), 2.90–2.96 (m, 1H, diastereotopic CH_2N), 3.62–3.69 (dq, 1H, CHP), 3.99–4.18 (m, 4H, $POCH_2$), 7.14–7.32 (m, 7H, aromatic H), 7.69 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 22.52; positive ion ESMS: calculated: $C_{21}H_{32}O_5N_2P_1S_1$ *m/z* (M + H) 455.2 and $C_{21}H_{31}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 477.2. Found: $C_{21}H_{32}O_5N_2P_1S_1$ *m/z* (M + H) 455.1 and $C_{21}H_{31}O_5N_2P_1S_1Na_1$ *m/z* (M + Na) 477.1. Chiral HPLC was conducted after derivatization with 3,5-dinitrobenzoylchloride to afford **24**.

4.10. General method for 3,5-dinitrobenzoylation of amines 17, 18, 21, and 22 for chiral HPLC analysis

4.10.1. Diethyl (1*R*)-2-amino-1-{[(4-methylphenyl)sulfonyl]-[3,5-dinitrobenzoyl-amino]}ethylphosphonate 19. A mixture of diethyl (1*R*)-2-amino-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate **17** (10.2 mg, 0.0290 mmol) and 3,5-dinitrobenzoyl chloride (8.4 mg, 0.0363 mmol) and Et_3N (5.1 μL, 0.0363 mmol) in 0.25 mL of CH_2Cl_2 were stirred overnight. TLC monitoring using 1:5 MeOH/$CHCl_3$ revealed the absence of starting amine. The reaction mixture was applied directly to one glass backed silica gel TLC plate and eluted with EtOAc. The major UV active band (R_f 0.39) was removed and the silica eluted with 1:5 MeOH/$CHCl_3$ to afford, following evaporation in vacuo, 9.8 mg (88% yield) of **19** as an oil. ^1H NMR ($CDCl_3$) δ 1.21–1.28 (m, 6H, CH_3), 2.35 (s, 3H, CH_3), 3.58–3.67 (m, 1H, diastereotopic CH_2N), 3.72–3.81 (m, 1H, diastereotopic CH_2N), 3.98–4.18 (m, 5H, OCH_2 and CHP), 6.47 (br s, 1H, NH), 7.24 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.76 (d, 2H, $J = 8.2$ Hz, aromatic H), 8.14 (br s, 1H, NH), 9.03 (d, 2H, $J = 2.0$ Hz, aromatic H), 9.11 (t, 1H, $J = 2.0$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 20.71; positive ion ESMS: calculated: $C_{20}H_{25}O_{10}N_4P_1S_1Na_1$ *m/z* (M + Na) 567.1, $C_{40}H_{50}O_{20}N_8P_2S_2Na_1$ *m/z* (2M + Na) 1111.2 and $C_{60}H_{75}O_{30}N_{12}P_3S_3Na_1$ *m/z* (3M + Na) 1655.3. Found: $C_{20}H_{25}O_{10}N_4P_1S_1Na_1$ *m/z* (M + Na) 567.1 (82%), $C_{40}H_{50}O_{20}N_8P_2S_2Na_1$ *m/z* (2M + Na) 1110.7 (100%) and $C_{60}H_{75}O_{30}N_{12}P_3S_3Na_1$ *m/z* (3M + Na) 1654.2 (10%); chiral HPLC with detection at 254 nm using a Chirex® column eluting at 1.0 mL/min with 20% 2-propanol in hexanes produced no separation. However, excellent separation occurred using a Whelk O-2 column 10:120:40: 2-propanol/hexanes/1,2-dichloroethane to afford a 99:1 ratio of L:D-enantiomers (L-t_R = 24.65 min and D-t_R = 35.77 min) or 98% ee.

4.10.2. Characterization data for diethyl (1*S*)-2-amino-1-{[(4-methylphenyl)sulfonyl]-[3,5-dinitrobenzoyl-amino]}-ethylphosphonate 20. 86% yield; ^1H NMR ($CDCl_3$) δ 1.21–1.28 (m, 6H, CH_3), 2.35 (s, 3H, CH_3), 3.58–3.67 (m, 1H, diastereotopic CH_2N), 3.71–3.81 (m, 1H, diastereotopic CH_2N), 3.98–4.18 (m, 5H, OCH_2 and CHP), 6.45 (dd, 1H, $J = 3.3$ and 9.1 Hz, NH), 7.24 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.76 (d, 2H, $J = 8.2$ Hz, aromatic H), 8.14 (t, 1H, $J = 5.4$ Hz, NH), 9.03 (d, 2H, $J = 2.0$ Hz, aromatic H), 9.12 (t, 1H, $J = 2.0$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 20.71; positive ion ESMS: Calculated: $C_{20}H_{25}O_{10}N_4P_1S_1Na_1$ *m/z* (M + Na) 567.1, $C_{40}H_{50}O_{20}N_8P_2S_2Na_1$ *m/z* (2M + Na) 1111.2 and $C_{60}H_{75}O_{30}N_{12}P_3S_3Na_1$ *m/z* (3M + Na) 1655.3. Found: $C_{20}H_{25}O_{10}N_4P_1S_1Na_1$ *m/z* (M + Na) 567.1 (55%), $C_{40}H_{50}O_{20}N_8P_2S_2Na_1$ *m/z* (2M + Na) 1110.8 (100%) and $C_{60}H_{75}O_{30}N_{12}P_3S_3Na_1$ *m/z* (3M + Na) 1654.1 (15%); Chiral HPLC with detection at 254 nm using a Chirex® column eluting at 1.0 mL/min with 20% 2-propanol in hexanes produced no separation. However, excellent separation occurred using a Whelk O-2 column 10:120:40: 2-propanol/hexanes/1,2-dichloroethane to afford a 98:2 ratio of L:D-enantiomers (L-t_R = 26.42 min and D-t_R = 30.82 min) or 96% ee.

4.10.3. Characterization data for diethyl (1*R*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-[(2-phenylethyl)-(3,5-dinitrobenzoyl)amino]ethylphosphonate 23. 89% yield; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3H, $J = 7.1$ Hz, CH_3), 1.88 (t, 3H, $J = 7.1$ Hz, CH_3), 2.43 (s, 3H, CH_3), 2.76 (t, 3H, $J = 6.0$ and 6.2 Hz, $ArCH_2$), 3.67–4.15 (m, 8H, CH_2N

and OCH_2), 4.25–4.37 (m, 1H, CHP), 5.70 (dd, 1H, $J = 4.5$ and 9.3 Hz, NH), 6.83 (d, 2H, $J = 8.0$ Hz, aromatic H), 7.15–7.36 (m, 5H, aromatic H), 7.78 (d, 2H, $J = 8.3$ Hz, aromatic H), 8.21 (d, 2H, $J = 2.0$ Hz, aromatic H), 8.93 (t, 1H, $J = 2.1$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 20.81; positive ion ESMS: calculated: $C_{28}H_{33}O_{10}N_4P_1S_1Na_1$ *m/z* (M + Na) 671.2 and $C_{56}H_{66}O_{20}N_8P_2S_2Na_1$ *m/z* (2M + Na) 1319.3. Found: $C_{28}H_{33}O_{10}N_4P_1S_1Na_1$ *m/z* (M + Na) 671.1 (100%) and $C_{56}H_{66}O_{20}N_8P_2S_2Na_1$ *m/z* (2M + Na) 1318.8 (20%). Chiral HPLC with detection at 254 nm using a Chirex® column eluting at 1.0 mL/min with 20% 2-propanol in hexanes produced very poor separation. However, surprisingly, excellent separation occurred using a Whelk O-2 column 10:120:40: 2-propanol/hexanes/1,2-dichloroethane at 2 mL/min to afford a 98:2 ratio of (*R*):(*S*)-enantiomers (*R*)-t_R = 21.82 min and (*S*)-t_R = 13.32 min) or 96% ee.

4.10.4. Characterization data for diethyl (1*S*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-[(2-phenylethyl)-(3,5-dinitrobenzoyl)amino] ethylphosphonate 24. 80% yield; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, $J = 7.1$ Hz, CH_3), 1.27 (t, 3H, $J = 7.1$ Hz, CH_3), 2.43 (s, 3H, CH_3), 2.76 (t, 3H, $J = 6.0$ Hz, $ArCH_2$), 3.68–4.15 (m, 8H, CH_2N and OCH_2), 4.25–4.37 (m, 1H, CHP), 5.55–5.58 (br m, 1H, NH), 6.84 (d, 2H, $J = 6.8$ Hz, aromatic H), 7.16–7.37 (m, 5H, aromatic H), 7.78 (d, 2H, $J = 8.2$ Hz, aromatic H), 8.21 (d, 2H, $J = 2.0$ Hz, aromatic H), 8.93 (t, 1H, $J = 2.0$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 20.79; positive ion ESMS: calculated: $C_{28}H_{33}O_{10}N_4P_1S_1Na_1$ *m/z* (M + Na) 671.2 and $C_{56}H_{66}O_{20}N_8P_2S_2Na_1$ *m/z* (2M + Na) 1319.3. Found: $C_{28}H_{33}O_{10}N_4P_1S_1Na_1$ *m/z* (M + Na) 671.2 (100%) and $C_{56}H_{66}O_{20}N_8P_2S_2Na_1$ *m/z* (2M + Na) 1318.9 (34%). Chiral HPLC with detection at 254 nm using a Chirex® column eluting at 1.0 mL/min with 20% 2-propanol in hexanes produced very poor separation. However, excellent separation occurred using a Whelk O-2 column 10:120:40: 2-propanol/hexanes/1,2-dichloroethane at 2 mL/min to afford a 1:99 ratio of L:D-enantiomers L-t_R = 22.45 min and D-t_R = 12.32 min) or 98% ee.

4.11. General method for the addition of imidazole to aziridines

4.11.1. Diethyl (1*R*)-2-(1*H*-imidazol-1-yl)-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 25. To L-aziridine **1** (50.0 mg, 0.1496 mmol) was added imidazole (39.0 mg, 0.5611 mmol) in 1 mL of CH_3CN. TLC monitoring indicated after 72 h that all starting **1** had been consumed. The reaction was diluted with 20 mL of EtOAc and 10 mL of water. The aqueous phase was extracted with two 10 mL portions of 2:5 *n*-BuOH/EtOAc. The solvent was removed in vacuo with the aid of a vacuum pump to afford 77 mg of an oil. The residue was purified by preparative thin-layer chromatography eluting with 1:10 MeOH/$CHCl_3$ containing 0.1% NH_4OH. The major UV positive band (R_f 0.38) was removed and eluted with 1:5 MeOH/$CHCl_3$ containing 0.1% NH_4OH to afford 47 mg (78% yield) of **25** as an oil. $[\alpha]_D^{20} = +18.5$ (*c* 0.740, $CHCl_3$); IR (TF) 3400–2200 (br), 3140, 3035, 2995, 2965, 1608, 1535, 1450, 1400, 1340, 1240, 1170, 1030, 960, 835, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19–1.27 (m, 6H, CH_3CH_2OP), 2.41 (s, 3H, CH_3), 3.93–4.30 (m, 7H, CH_2ON, CHP, $POCH_2$), 6.88 (d, 2H, $J = 5.8$ Hz, NCHCHN imidazoyl), 7.26 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.44 (s, 1H, NCHN imidazoyl), 7.67 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.09–16.24 (m, CH_3CH_2OP), 21.40, 46.76 (d, $J_{CCP} = 5.4$ Hz, CH_2CHP), 51.03 (d, $J_{CP} = 157.6$ Hz, CHP), 62.85 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 63.93 (d, $J_{COP} = 7.0$ Hz, CH_3CH_2OP), 119.54, 126.68, 128.78, 129.63, 137.98, 138.08, 143.46; ^{31}P NMR ($CDCl_3$) δ 19.83; positive ion ESMS: calculated: $C_{16}H_{25}O_5N_3P_1S_1$ *m/z* (M + H) 402.1. Found: $C_{16}H_{25}O_5N_3P_1S_1$ *m/z* (M + H) 402.1. Chiral HPLC failed due to severe broadening under conditions and columns attempted.

4.11.2. Characterization data for diethyl (1*S*)-2-(1*H*-imidazol-1-yl)-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 26. 68% yield; $[\alpha]_D^{20} = -13.3$ (*c* 0.744, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.19–1.25 (m, 6H, CH_3CH_2OP), 2.42 (s, 3H, CH_3), 3.92–4.12 (m, 5H, CHP and $POCH_2$), 4.25–4.30 (m, 2H, CH_2N), 6.94 (d, 2H, $J = 6.9$ Hz, NCHCHN imidazoyl), 7.29 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.56 (s, 1H, NCHN imidazoyl), 7.69 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 19.55; positive ion ESMS: calculated: $C_{16}H_{25}O_5N_3P_1S_1$ *m/z* (M + H) 402.1. Found: $C_{16}H_{25}O_5N_3P_1S_1$ *m/z* (M + H) 402.1. Chiral HPLC failed due to severe broadening under conditions and columns attempted.

4.12. General procedures for the addition of thiols to aziridines

4.12.1. Diethyl (1*R*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-(propylsulfanyl)ethylphosphonate 27. To an ambient room temperature solution of *n*-propylthiol (17 μL, 0.1795 mmol) and L-aziridine **1** (50.0 mg, 0.1496 mmol) in 1.0 mL of CH_3CN was added by syringe tri-*n*-butylphosphine (36 μL, 0.1496 mmol). The reaction was stirred overnight. CH_3CN was evaporated in vacuo and the residue purified by silica TLC eluting with 2:1 ethylacetate/hexanes to afford 22.2 mg (36% yield) of **27** as an oil. $[\alpha]_D^{20} = -19.3$ (*c* 0.344, $CHCl_3$); IR (TF) 3140 (br), 2995, 2920, 1602, 1460, 1345, 1245, 1170, 1100, 1050, 1030, 980, 825, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 7.3$ Hz, CH_3), 1.29 (t, 6H, $J = 7.0$ Hz, CH_3CH_2OP), 1.42–1.52 (m, 2H, CH_2), 2.34 (t, 3H, $J = 7.3$ Hz, SCH_2), 2.42 (s, 3H, CH_3), 2.70–2.84 (m, 2H, CH_2S), 3.81–3.92 (m, 1H, CHP), 4.03–4.21 (m, 4H, $POCH_2CH_3$), 5.62 (dd, 1H, $J = 3.1$ and 9.3 Hz, NH), 7.29 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.80 (d, 2H, $J = 8.2$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 13.30, 16.23–16.40 (m, CH_3CH_2OP), 21.48, 22.62, 32.99 (d, $J_{CCP} = 4.3$ Hz, CH_2CHP), 34.99, 49.93 (d, $J_{CP} = 159.0$ Hz, CHP), 62.80 (d, $J_{COP} = 7.0$ Hz, CH_3CH_2OP), 63.53 (d, $J_{COP} = 6.6$ Hz, CH_3CH_2OP), 127.19, 129.47, 138.06, 143.47; ^{31}P NMR ($CDCl_3$) δ 21.69 ppm; positive ion ESMS: calculated: $C_{16}H_{28}O_5N_1P_1S_2Na_1$ *m/z* (M + Na) 432.1. Found: $C_{16}H_{28}O_5N_1P_1S_2Na_1$ *m/z* (M + Na) 432.1 (100%). Chiral HPLC using a Whelk O-2 column was unsuccessful under a variety of conditions.

4.12.2. Characterization data for diethyl (1*S*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-(propylsulfanyl)ethylphosphonate 28. 43% yield; $[\alpha]_D^{20} = +18.0$ (*c* 0.128, $CHCl_3$); IR (TF) 3140 (br), 2995, 2940, 1610, 1470, 1330, 1250, 1175, 1105, 1040, 985, 830, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 7.3$ Hz, CH_3), 1.25–1.31 (m, 6H, CH_3CH_2OP), 1.43–1.52 (m, 2H, CH_2), 2.35 (t, 3H, $J = 7.3$ Hz, SCH_2), 2.42 (s, 3H, CH_3), 2.70–2.84 (m, 2H, CH_2S), 3.81–3.92 (m, 1H, CHP), 4.03–4.22 (m, 4H, $POCH_2CH_3$), 5.44–5.47 (m, 1H, NH), 7.29 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.79 (d, 2H, $J = 8.2$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 21.66 ppm; positive ion ESMS: calculated: $C_{16}H_{28}O_5N_1P_1S_2Na_1$ *m/z* (M + Na) 432.1. Found: $C_{16}H_{28}O_5N_1P_1S_2Na_1$ *m/z* (M + Na) 432.1 (100%). Chiral HPLC using a Whelk O-2 column was unsuccessful under a variety of conditions.

4.12.3. Diethyl (1*R*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-(triphenylmethylsulfanyl)ethylphosphonate 29

4.12.3.1. Sodium hydride derived thiolate reaction. To an ambient room temperature solution of triphenylmethylmercaptan (42 mg, 0.1496 mmol) in 2 mL of THF was added 60% NaH (6.0 mg, 0.1496 mmol). This was stirred for 5 min at which time H_2 evolution had ceased. L-Aziridine **1** (50 mg, 0.1496 mmol) in 1.0 mL of THF was added via syringe followed by stirring overnight. The THF was evaporated in vacuo and the residue dissolved in 20 mL of EtOAc and washed with brine, dried, filtered, and evaporated in vacuo to afford 96 mg of an oil. This oil was purified by silica gel column chromatography (20 mL silica gel) eluting with 2:1 EtOAc/hexanes to afford 27.3 mg. Impure fractions were further purified by analytical silica TLC using the same solvent. Three purified fractions were obtained: 1. $R_f = 0.63$, 32 mg (36% yield) of desired sulfide **29**; 2. $R_f = 0.54$, 5 mg (5% yield) of the disulfide **31** and 13 mg (26% recovery) of unreacted L-aziridine **1**: The desired sulfide product **29** was a foam that resisted all attempts at recrystallization: mp 61–63 °C; $[\alpha]_D^{20} = +1.4$ (*c* 1.00, $CHCl_3$); IR (TF) 3110 (br), 3040, 2995, 2920, 1602, 1500, 1455, 1345, 1245, 1170, 1100, 1060, 1035, 985, 840, 735, 710, 675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16–1.29 (m, 6H, CH_3CH_2OP), 2.32–2.41 (m, 1H, diastereotopic CH_2S), 2.34 (s, 3H, CH_3), 2.46–2.54 (m, 1H, diastereotopic CH_2S), 3.56–3.67 (m, 1H, CHP), 3.90–4.14 (m, 4H, $POCH_2CH_3$), 4.92 (dd, 1H, $J = 3.8$ and 9.4 Hz, NH), 7.13–7.30 (m, 17H, aromatic H), 7.72 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.18–16.37 (m, CH_3CH_2OP), 21.52, 32.85 (d, $J_{CCP} = 7.0$ Hz, CH_2CHP), 49.86 (d, $J_{CP} = 156.5$ Hz, CHP), 62.76 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 63.52 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 67.00, 126.71, 126.97, 127.05, 127.29, 127.39, 127.87, 129.21, 129.27, 129.46, 130.02, 137.96, 143.24, 144.23; ^{31}P NMR ($CDCl_3$) δ 21.06; positive ion ESMS: calculated: $C_{32}H_{36}O_5N_1P_1S_2Na_1$ *m/z* (M + Na) 632.2, $C_{32}H_{36}O_5N_1P_1S_2K_1$ *m/z* (M + K) 648.1 and $C_{64}H_{72}O_{10}N_2P_2S_4Na_1$ *m/z* (2M + Na) 1241.3. Found: $C_{32}H_{36}O_5N_1P_1S_2Na_1$ *m/z* (M + Na) 632.1 (100%), $C_{32}H_{36}O_5N_1P_1S_2K_1$ *m/z* (M + K) 648.1 (50%) and $C_{64}H_{72}O_{10}N_2P_2S_4Na_1$ *m/z* (2M + Na) 1240.9 (25%). Chiral HPLC using a Whelk O-2 column was unsuccessful under a variety of conditions.

4.12.4. Characterization data for diethyl (1*R*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-(triphenylmethyl-disulfanyl)ethylphosphonate 31. $[\alpha]_D^{20} = -59.1$ (*c* 0.310, $CHCl_3$); IR (TF) 3110 (br), 3045, 2995, 2910, 1602, 1500, 1450, 1345, 1245, 1170, 1100, 1060, 1035, 970, 825, 745, 710, 675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23–1.28 (m, 6H, CH_3CH_2OP), 1.92–2.09 (m, 2H, CH_2SS), 2.36 (s, 3H, CH_3), 3.58–3.70 (m, 1H, CHP), 3.93–4.15 (m, 4H, $POCH_2CH_3$), 4.82 (dd, 1H, $J = 3.3$ and 9.6 Hz, NH), 7.13–7.31 (m, 17H, aromatic H), 7.72 (d, 2H, $J = 8.4$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.27–16.43 (m, CH_3CH_2OP), 21.49, 38.84 (d, $J_{CCP} = 5.6$ Hz, CH_2CHP), 49.72 (d, $J_{CP} = 157.9$ Hz, CHP), 62.65 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 63.61 (d, $J_{COP} = 7.2$ Hz, CH_3CH_2OP), 71.22, 126.97, 127.05, 127.21, 127.31, 127.84, 129.22, 129.25, 129.95, 130.27, 137.92, 143.47, 143.50; ^{31}P NMR ($CDCl_3$) 20.97; positive ion ESMS: calculated: $C_{13}H_{21}O_5N_1P_1S_3Na_1$ *m/z* (M − $C(C_6H_5)_3$ + Na) 421.0, $C_{32}H_{36}O_5N_1P_1S_3Na_1$ *m/z* (M + Na) 664.1 and $C_{64}H_{72}O_{10}N_2P_2S_6Na_1$ *m/z* (2M + Na) 1305.3. Found: $C_{13}H_{21}O_5N_1P_1S_3Na_1$ *m/z* (M − $C(C_6H_5)_3$ + Na) 420.9, $C_{32}H_{36}O_5N_1P_1S_3Na_1$ *m/z* (M + Na) 663.9 and $C_{64}H_{72}O_{10}N_2P_2S_6Na_1$ *m/z* (2M + Na) 1304.8.

4.12.4.1. Tri-*n*-butylphosphine reaction. To an ambient room temperature solution of triphenylmethylmercaptan (2.69 g, 9.722 mmol) and L-aziridine **1** (2.71 g, 8.102 mmol) in 30 mL of CH_3CN was added by syringe tri-*n*-butylphosphine (2.0 mL, 8.102 mmol). The suspension was stirred overnight. CH_3CN was evaporated in vacuo and the residue purified by silica gel column chromatography (500 mL silica gel) eluting with 2:1 EtOAc/hexanes to afford 2.26 g (46% yield) of **29** as a white foam. This material was spectroscopically identical to the material described above. There was no sign of the presence of the undesired disulfide product **31** or recovered aziridine **1**.

4.12.5. Diethyl (1*S*)-1-{[(4-methylphenyl)sulfonyl]amino}-2-(triphenylmethylsulfanyl)ethylphosphonate 30. 78% yield. This foam resisted all attempts at recrystallization. Mp 61–63 °C; $[\alpha]_D^{20} = -1.4$ (*c* 0.580, $CHCl_3$); IR (TF) 3110 (br), 3040, 2995, 2920, 1602, 1495, 1450, 1340, 1240, 1165, 1095, 1030, 980, 820, 750, 705, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16–1.25 (m, 6H, CH_3CH_2OP), 2.30–2.51 (m, 2H, CH_2S), 2.33 (s, 3H, CH_3), 3.54–3.66 (m, 1H, CHP), 3.90–4.14 (m, 4H, $POCH_2CH_3$), 5.18 (dd, 1H, $J = 3.3$ and 9.4 Hz, NH), 7.14–7.29 (m, 17H, aromatic H), 7.72 (d, 2H, $J = 8.1$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 21.11; positive ion ESMS: calculated: $C_{32}H_{36}O_5N_1P_1S_2Na_1$ *m/z* (M + Na) 632.2 and $C_{64}H_{72}O_{10}N_2P_2S_4Na_1$ *m/z* (2M + Na) 1241.3. Found: $C_{32}H_{36}O_5N_1P_1S_2Na_1$ *m/z* (M + Na) 632.1 (55%) and $C_{64}H_{72}O_{10}N_2P_2S_4Na_1$ *m/z* (2M + Na) 1241.0 (100%). Chiral HPLC using a Whelk O-2 column was unsuccessful under a variety of conditions.

4.13. General procedure for the reaction of $NaBH_4$ with aziridines

4.13.1. Diethyl (1*R*)-1-{[(4-methylphenyl)sulfonyl]amino}-ethylphosphonate 32. To L-aziridine **1** (2.40 g, 7.19 mmol) in 25 mL of THF was added in one portion $NaBH_4$ (0.29 g, 7.545 mmol). The reaction was stirred for 18 h and THF evaporated in vacuo. The residue was diluted with 100 mL of EtOAc and 50 mL of water containing 3 mL of glacial AcOH. The aqueous phase was extracted with two 50 mL portions of EtOAc. The pooled organic phases were washed with brine, dried, filtered, and evaporated in vacuo to afford 2.54 g of a semi-solid. This was purified by radial silica gel chromatography using a 4 mm plate eluting with EtOAc to afford 2.33 g (96%) of **32** as an oil. The same product could be obtained by catalytic transfer hydrogenation in 50% yield. $[\alpha]_D^{20} = -17.0$ (*c* 1.00, $CHCl_3$); IR (TF) 3115 (br), 3010, 2965, 1610, 1460, 1405, 1350, 1245, 1175, 1035, 970, 830, 790, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (dd, 3H, $J = 7.2$ and 16.9 Hz, CH_3), 1.25–1.33 (m, 6H, CH_3CH_2OP), 2.42 (s, 3H, CH_3), 3.60–3.74 (m, 1H, CHP), 4.01–4.26 (m, 4H, $POCH_2$), 6.14 (dd, 1H, $J = 2.4$ and 9.4 Hz, NH), 7.28 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.80 (d, 2H, $J = 8.4$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 15.79, 16.23–16.42 (m, CH_3CH_2OP), 21.44, 45.91 (d, $J_{CP} = 162$ Hz, CHP), 62.39 (d, $J_{COP} = 7.2$ Hz, CH_3CH_2OP), 63.74 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 128.01, 129.55, 133.36, 143.26; ^{31}P NMR ($CDCl_3$) δ 24.06; positive ion ESMS: calculated: $C_{13}H_{23}O_5N_1P_1S_1$ *m/z* (M + H) 336.1, $C_{13}H_{22}O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 358.1, $C_{13}H_{22}O_5N_1P_1S_1K_1$ *m/z* (M + K) 374.1. Found: $C_{13}H_{23}O_5N_1P_1S_1$ *m/z* (M + H) 336.0 (64%), $C_{13}H_{22}O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 358.1 (100%), $C_{13}H_{22}O_5N_1P_1S_1K_1$ *m/z* (M + K) 374.0 (24%). Chiral HPLC using a Whelk O-2 column eluting with 20% 2-propanol in hexanes at 1.0 mL/min to afforded a 99:1 ratio of L:D-enantiomers (L-t_R = 18.22 min and D-t_R = 21.55 min).

4.13.2. Characterization data for diethyl (1*S*)-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 33. 54% yield; $[\alpha]_D^{20} = +15.0$ (*c* 0.276, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.19 (dd, 3H, $J = 7.2$ and 16.8 Hz, CH_3), 1.25–1.33 (m, 6H, CH_3CH_2OP), 2.42 (s, 3H, CH_3), 3.60–3.74 (m, 1H, CHP), 4.01–4.24 (m, 4H, $POCH_2$), 5.61 (dd, 1H, $J = 3.0$ and 9.4 Hz, NH), 7.30 (d, 2H, $J = 8.2$ Hz, aromatic H), 7.78 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 24.11; positive ion ESMS: calculated: $C_{13}H_{22}O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 358.1. Found: $C_{13}H_{22}O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 358.1. Chiral HPLC using a Whelk O-2 column eluting with 20% 2-propanol in hexanes at 1.0 mL/min to afford an undetectable amount of the L-enantiomer (D-t_R = 20.07 min).

4.14. General procedure for the reaction of $(n\text{-Bu})_4NF$ with aziridines

4.14.1. Diethyl (1*R*)-2-fluoro-1-[(4-methylphenyl)sulfonyl]aminoethylphosphonate 34. To a solution of L-aziridine **1** (50.0 mg, 0.1496 mmol) in 1.0 mL of THF was added by syringe 1.0 M tetrabutylammonium fluoride in THF (0.16 mL, 0.1571 mmol). The reaction was stirred overnight and then diluted with 20 mL of EtOAc and 10 mL of water. The aqueous phase was extracted with two 5 mL of EtOAc. The pooled organic layer was washed with brine, dried, filtered, and evaporated in vacuo to afford 50.8 mg of residue that was purified by silica TLC. Two elutions with 2:1 ethylacetate/hexanes afforded 28.0 mg (53% yield) of **34** as an oil. $[\alpha]_D^{20} = -11.2$ (*c* 0.366, $CHCl_3$); IR (TF) 3140 (br), 2995, 2920, 1602, 1465, 1350, 1250, 1180, 1040, 830, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–1.31 (m, 6H, CH_3CH_2OP), 2.42 (s, 3H, CH_3), 3.80–3.97 (m, 1H, CHP), 4.03–4.23 (m, 4H, $POCH_2CH_3$), 4.35–4.68 (m, 2H, CH_2F), 5.93 (dd, 1H, $J = 3.8$ and 9.5 Hz, NH), 7.29 (d, 2H, $J = 8.4$ Hz, aromatic H), 7.78 (d, 2H, $J = 8.3$ Hz, aromatic H); ^{13}C NMR ($CDCl_3$) 16.15–16.35 (m, CH_3CH_2OP), 21.47, 50.94 (dd, $J_{CP} = 156.7$ Hz and $J_{FCCP} = 20.9$ Hz, CHP), 62.98 (d, $J_{COP} = 7.1$ Hz, CH_3CH_2OP), 63.79 (d, $J_{COP} = 6.9$ Hz, CH_3CH_2OP), 81.81 (dd, $J_{CF} = 175.3$ Hz and $J_{FCCP} = 2.4$ and 2.9 Hz, CH_2F), 127.05, 129.57, 137.85, 143.60; ^{31}P NMR ($CDCl_3$) δ 19.10 (d, $J_{FCCP} = 20.0$ Hz); ^{19}F NMR ($CDCl_3$) 100.03–100.41 (m); positive ion ESMS: calculated: $C_{13}H_{22}F_1O_5N_1P_1S_1$ *m/z* (M + H) 354.1 and $C_{13}H_{21}F_1O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 376.1. Found: $C_{13}H_{22}F_1O_5N_1P_1S_1$ *m/z* (M + H) 354.0 and $C_{13}H_{21}F_1O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 376.1. Chiral HPLC using a Whelk O-2 column was unsuccessful under a variety of conditions.

4.14.2. Characterization data for diethyl (1*S*)-2-fluoro-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 35. 57% yield; $[\alpha]_D^{20} = +10.2$ (*c* 1.200, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.23–1.33 (m, 6H, CH_3CH_2OP), 2.43 (s, 3H, CH_3), 3.78–3.95 (m, 1H, CHP), 4.01–4.22 (m, 4H, $POCH_2CH_3$), 4.35–4.70 (m, 2H, CH_2F), 5.51 (dd, 1H, $J = 4.0$ and 9.4 Hz, NH), 7.30 (d, 2H, $J = 8.1$ Hz, aromatic H), 7.77 (d, 2H, $J = 8.2$ Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 19.09 (d, $J_{FCCP} = 18.4$ Hz); ^{19}F NMR ($CDCl_3$) δ 100.14–100.51 (m); positive ion ESMS: calculated: $C_{13}H_{21}F_1O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 376.1. Found: $C_{13}H_{21}F_1O_5N_1P_1S_1Na_1$ *m/z* (M + Na) 376.1. Chiral HPLC using a Whelk O-2 column was unsuccessful under a variety of conditions.

4.15. General procedure for the reaction of lithium diethylphosphite with aziridines

4.15.1. Diethyl (1*R*)-(2-diethylphosphoryl)-1-{[(4-methylphenyl)sulfonyl]amino} ethylphosphonate 36. To a solution of freshly distilled diethylphosphite (52 mg, 0.3740 mmol) in 1 mL of THF at 0 °C was added via syringe 2.29 M *n*-butyllithium (82 μL, 0.1870 mmol). The cooling bath was removed and the mixture stirred for 1.25 h. This anion solution was transferred via canula to L-aziridine **1** (50 mg, 0.1496 mmol) with the aid of 1 mL of THF. The solution was stirred overnight. The reaction was diluted with 20 mL of EtOAc and washed with a mixture of 10 mL of brine and 0.5 mL of 1 M AcOH. The aqueous phase was extracted with two 15 mL portions of EtOAc and the pooled organic phases dried, filtered, and evaporated in vacuo to afford 84.8 mg of residue. This was purified by preparative TLC eluting twice with 1:20 MeOH/$CHCl_3$. The

R_f = 0.37 band was removed and eluted with 1:5 MeOH/$CHCl_3$ followed by evaporation to afford 45 mg (64% yield) of **36** as an oil. $[\alpha]_D^{20} = -3.7$ (*c* 0.810, $CHCl_3$); IR (TF) 3120 (br), 2995, 2920, 1602, 1450, 1400, 1340, 1250, 1170, 1040 (br), 975, 820, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12–1.33 (m, 12H, CH_3CH_2OP), 1.93–2.18 (m, 2H, CH_2P), 2.41 (s, 3H, CH_3), 3.86–4.22 (m, 9H, CHP and $POCH_2CH_3$), 6.32 (dd, 1H, J = 1.7 and 9.4 Hz, NH), 7.29 (d, 2H, J = 7.8 Hz, aromatic H), 7.82 (d, 2H, J = 8.3 Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 16.00–16.35 (m, CH_3CH_2OP), 21.40, 25.72 (dd, J_{CP} = 142.0 Hz and J_{PCCP} = 3.7 Hz, CH_2P), 45.90 (dd, J_{CP} = 165.4 Hz and J_{PCCP} = 5.4 Hz, CHP), 61.82 (d, J_{COP} = 6.3 Hz, CH_3CH_2OP), 62.26 (d, J_{COP} = 6.6 Hz, CH_3CH_2OP), 62.85 (d, J_{COP} = 6.8 Hz, CH_3CH_2OP), 63.69 (d, J_{COP} = 7.3 Hz, CH_3CH_2OP), 127.19, 129.37, 138.28, 143.26; ^{31}P NMR ($CDCl_3$) δ 20.87 (d, J_{PCCP} = 31.0 Hz), 26.21 (d, J_{PCCP} = 31.0 Hz); positive ion ESMS: calculated: $C_{17}H_{31}O_8N_1P_2S_1Na_1$ *m/z* (M + Na) 494.1 and $C_{34}H_{62}O_8N_1P_2S_1Na_1$ *m/z* (2M + Na) 965.2. Found: $C_{17}H_{31}O_8N_1P_2S_1Na_1$ *m/z* (M + Na) 494.0 (100%) and $C_{34}H_{62}O_8N_1P_2S_1Na_1$ *m/z* (2M + Na) 965.2 (10%). Chiral HPLC using a Whelk O-2 column was unsuccessful under a variety of conditions.

4.15.2. Characterization data for diethyl (1*S*)-(2-diethylphosphoryl)-1-{[(4-methylphenyl)sulfonyl]amino}ethylphosphonate 37. 33% yield; $[\alpha]_D^{20} = +4.1$ (*c* 0.924, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20–1.32 (m, 12H, CH_3CH_2OP), 1.90–2.16 (m, 2H, CH_2P), 2.42 (s, 3H, CH_3), 3.85–4.22 (m, 9H, CHP and $POCH_2CH_3$), 6.08 (dd, 1H, J = 1.9 and 9.4 Hz, NH), 7.30 (d, 2H, J = 7.8 Hz, aromatic H), 7.82 (d, 2H, J = 8.3 Hz, aromatic H); ^{31}P NMR ($CDCl_3$) δ 20.74 (d, J_{PCCP} = 28.7 Hz), 26.28 (d, J_{PCCP} = 28.7 Hz); positive ion ESMS: calculated: $C_{17}H_{31}O_8N_1P_2S_1Na_1$ *m/z* (M + Na) 494.1 and $C_{34}H_{62}O_8N_1P_2S_1Na_1$ *m/z* (2M + Na) 965.2. Found: $C_{17}H_{31}O_8N_1P_2S_1Na_1$ *m/z* (M + Na) 494.1 (100%) and $C_{34}H_{62}O_8N_1P_2S_1Na_1$ *m/z* (2M + Na) 964.9 (30%). Chiral HPLC using a Whelk O-2 column was unsuccessful under a variety of conditions.

4.15.3. Diethyl (1*R*)-1-{[(carbobenzyloxy]amino}ethylphosphonate 38. To 10 mL of double distilled (from sodium metal) liquid NH_3 at −78 °C were added sodium slivers (34 mg, 1.4782 mmol) and stirred for 5 min. To this blue solution was added dropwise via syringe tosylate **32** (100 mg, 0.2985 mmol) in a total of 1.5 mL of anhydrous THF. This mixture was stirred for 10 min followed by quenching by addition of 1 mL of absolute EtOH. The NH_3 was evaporated under a stream of nitrogen and the ethanol evaporated in vacuo. To this residue was added 2 mL of water and solid $NaHCO_3$ (125 mg, 1.4925 mmol) followed by Cbz-Cl (62 mg, 0.3582 mmol) in 2 mL of THF. This mixture was stirred for 2 h followed by evaporation of THF. The residue was transferred to a separatory funnel with 15 mL of EtOAc and 5 mL of brine. The aqueous phase was extracted with 2 × 15 mL of EtOAc. The pooled organic phases were dried, filtered, and evaporated. The crude product was purified by preparative silica TLC eluting with EtOAc to afford 65 mg (68% yield) of **38** as an oil. $[\alpha]_D^{20} = -12.5$ (*c* 1.18, $CHCl_3$); IR (TF) 3215 (br), 3005, 2990, 2915, 1715, 1530, 1450, 1390, 1300, 1250, 1170, 1040 (br), 965, 800, 740, 700 cm^{-1}; ^1H NMR (d_6-DMSO) δ 1.15–1.28 (m, 9H, CH_3CH_2OP and CH_3), 3.87–4.10 (m, 5H, CHP and $POCH_2CH_3$), 5.04 (q, 2H, J = 23.7 Hz, benzylic CH_2), 7.30–7.39 (m, 5, aromatic H), 7.65 (d, 1H, J = 9.3 Hz, NH); ^{13}C NMR (d_6-DMSO) δ 15.15, 16.24 (t, J_{CCOP} = 4.3 and 4.6 Hz, CH_3CH_2OP), 42.85 (d, J_{CP} = 158 Hz, CHP), 61.59 (d, J_{COP} = 6.6 Hz, CH_3CH_2OP), 61.90 (d, J_{COP} = 6.8 Hz, CH_3CH_2OP), 65.53, 127.72, 127.79, 128.30, 137.00, 155.56 (d, $J_{CONHCHP}$ = 5.0 Hz, carbonyl); ^{31}P NMR (d_6-DMSO) δ 25.89; positive ion ESMS: calculated: $C_{14}H_{22}O_5N_1P_1Na_1$ *m/z* 338.1 (M + Na). Found: $C_{14}H_{22}O_5N_1P_1Na_1$ *m/z* 338.1 (M + Na). Chiral HPLC using a Whelk O-2 column eluting with 10:120:40: 2-propanol/hexanes/1,2-dichloromethane at 1 mL/min to afford a 95:5 ratio of (*R*):(*S*)-enantiomers (*R*)-t_R = 12.78 min and (*S*)-t_R = 10.42 min).

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