Alkylations of Chiral, Phosphoryl- and Thiophosphoryl-Stabilized Carbanions

Scott E. Denmark* and Chien-Tien Chen

Contribution from the Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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Abstract: A general method for the preparation of enantiomerically enriched phosphonic acids and phosphonates with three different α-substitution patterns (aryl, alkyl, and alkoxy) has been developed. Anions derived from enantiomerically enriched thiophosphonamidates (2-thioxo-1,3,2-oxazaphosphorinanes) underwent smooth electrophilic substitutions with excellent diastereoselectivity for both cis and trans stereoisomers. Highly enantioselective synthesis of α-alkoxyphosphonates in either antipodal form can be achieved by the employment of highly diastereoselective alkylation with anions derived from the corresponding *P*-methoxymethyl analogs in the presence of HMPA or PMDTA. Implications for the aggregation states and reactive conformations of the anions are discussed.

Introduction

Over the last two decades, the synthesis and utilization of phosphonic acids and phosphonate derivatives have emerged as areas of significant research interest. The potential for metabolic regulation (or inhibition), the interest in understanding microbial degradation pathways, and the use of phosphonates as possible surrogates for the corresponding phosphates and carboxylates highlight their importance in biological systems.[1] Particularly, those phosphonates possessing an α-amino substituent have been shown to exhibit significant biological activity.[2] Since it has been shown that the biological activity is highly dependent on the absolute configuration,[3] the asymmetric synthesis of α-substituted phosphonates is highly desirable for the evaluation of their action and of structure–activity relationships. Apart from reports that employ resolution technologies[4] or enzymes,[5] methods relying on the creation of the α-stereocenter in an asymmetric process have received attention only recently.

The application of phosphoryl-stabilized carbanions in carbonyl olefinations has achieved tremendous prominence in organic synthesis.[6] However, efforts aimed at developing the chemistry of these species not related to the olefin formation (e.g., electrophilic addition, substitution, and rearrangement) has been meager by comparison. In recent years, the potential for asymmetric variation at phosphorus has been recognized and explored to effect stereoselective asymmetric transformations in the context of carbonyl and imine additions, Michael additions, rearrangements, and olefination.[7] In addition to these advances, a limited number of investigations have appeared in the literature documenting electrophilic substitutions in a chiral environment. The asymmetric alkylations of anions derived from chiral phosphine oxides,[8] phosphonates,[9] phosphonamides,[10] phosphonamidates,[11] and Schiff bases[12] have been investigated and have individual advantages in many situations. However, many of these methods have lacked general ap-

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plicability and the levels of asymmetric induction have been highly electrophile dependent. To date, the synthesis of alkylphosphonic acids in either antipodal form by the alkylation of C_2-symmetric bicyclic phosphonamides derived from 1,2-cyclohexanediamine seems most promising in this respect.[10]

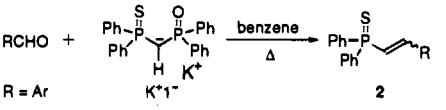
In striking contrast to the well-developed chemistry of phosphoryl-stabilized carbanions, there have been sparingly few reports associated with the chemistry of thiophosphoryl (P=S)-stabilized carbanions. In most instances, they have been utilized as complementary reagents to the corresponding phosphoryl analogs to effect stereoselective olefination[13] and alkylation.[14] Their potential availability for asymmetric transformation notwithstanding, there existed only one study documenting the utility of chiral phosphinothioic amide-stabilized carbanions in diastereoselective addition to racemic α-substituted ketones.[15]

Background

For the last decade, efforts aimed at elucidating the electronic nature of phosphoryl and thiophosphoryl bonds have led to seemingly diverse conclusions.[16] Three limiting bonding scenarios can be envisioned for describing the electron distribution between phosphorus and a chalcogen which differ in the formal designation of electron pair sharing and multiple bonds. Any such discussion, must bear in mind that the fortuitous correspondence between bond strength and number of electron pairs exists only among second-row elements and breaks down for lower rows. The P−O bond contains three electron pairs but has a bond strength of approximately two. Experimental evidence indicates a strong, short, and polar P−O bond with a bond order of greater than two and a somewhat weaker and less polar P−S bond with a bond order less than two.[17]

We have recently completed a comprehensive computational comparison of phosphoryl- and thiophosphoryl-stabilized carbanions and of the energetic and structural consequences of P−C bond rotation in acyclic and cyclic methylphosphonic and methylthioxophosphonic anions.[18] With electronegative elements bonded to phosphorus, the carbon substituents are oriented parallel to the P=X axis in the acyclic as well as in the cyclic compounds. This arrangement is corroborated by solution

Scheme 1



(NMR) and solid state (X-ray analysis) structures of the six-membered phosphorinanes (vide infra). The carbon lone pair is mainly stabilized by interaction with the σ* (P−Y) orbitals. In the transition state (TS) structures, the carbanion is strongly pyramidalized and the lone pair is oriented parallel to the P=X axis. The major stabilization of the carbon lone pair is through

X = O, S
Y = NH_2, F, $NH(CH_2)_2HN$, $NH(CH_2)_3HN$

the σ* (P=X) orbital. The different orientations of the amino groups in the acyclic systems yield a small difference (0.3 kcal/mol at MP4(SDQ)/6-31+G*//6-31+G* + ZPE) between P−C bond rotational barriers for the P=O and P=S species. However, in the difluoride and the cyclic systems, the activation barrier for P−C bond rotation is 1.8−2.4 kcal/mol higher for the P=S compared to the P=O compounds. A difference of 3.1 kcal/mol has been determined by variable-temperature NMR methods.[19] A detailed analysis of the electronic interactions evokes a superior ground state stabilization in the P=S compared to the P=O derivatives as the cause for the higher sulfur TS energies. This is supported by the isodesmic equation (eq 1) which yields a 5−8 kcal/mol stronger carbanion-stabilizing effect for the thio species.[18a] This leads to the prediction that thiophosphoryl anions should be more stable (i.e., stronger CH acids) than their phosphoryl counterparts.

$$CH_3{-}P(X)(Y)_2 + CH_3^- \rightarrow {}^-CH_2{-}P(X)(Y)_2 + CH_4 \quad (1)$$

$$(Y)_2 = NH_2, F, NH(CH_2)_{2/3}HN; X = O, S$$

There are very few direct experimental comparisions between phosphoryl- and thiophosphoryl-stabilized anions. In one, pK_A determinations (THF) have shown that the lithium salts of a phosphonate[20] and phosphine oxides[21] are more acidic than their thio analogs, which is inconsistent with the theoretical findings mentioned above. This apparent contradiction can be understood in terms of the neglected gegenion effect in eq 1 due to a stronger heteroatom−lithium contact compared to the C−Li interaction.[22] Indeed, if the counterion is included in the isodesmic equation, a distinct preference (ca. 10 kcal/mol) for the phosphoryl-stabilized carbanions emerges.[18a] In a second comparison, exclusive formation of alkenylphosphine sulfide **2** (64−76%) has been observed in an intramolecular competitive olefination of unsymmetrical methylenebis(phosphine) chalcogenide $K^+\mathbf{1}^-$ [23] Scheme 1.

This dramatic reactivity difference was further substantiated in an intermolecular competition experiment reported by Juaristi

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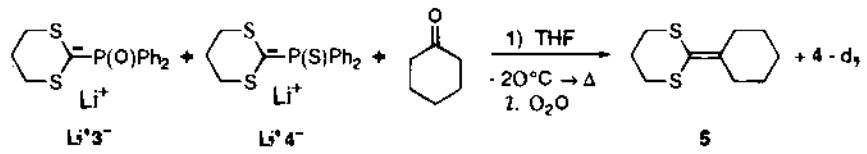
Scheme 2



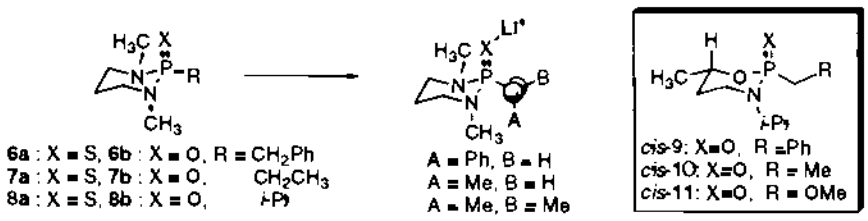


Figure 1. Phosphoryl- and thiophosphoryl-stabilized carbanionic reagents.

and co-workers.[21] Combination of 1 equiv each of 2-diphenylphosphinoyl and 2-(diphenylthiophosphinoyl)-2-(1,3)dithianyl carbanions Li^+**3**$^-$ and Li^+**4**$^-$ with cyclohexanone produced dithiane **5** in 67% along with recovered **3** (0.33 equiv) and **4** (1.0 equiv) (Scheme 2). The potential side reaction of enolate formation has been ruled out as evidenced by complete deuterium incorporation in recovered **4** when the reaction mixture was quenched with D_2O. These findings were interpreted to support the stronger polar nature of P=O bonds which can facilitate cycloelimination of the incipient β-oxyanionic phosphine oxide.

In recent years we have been involved in exploring the chemistry of phosphorus-stabilized anions with regard to structure,[19,24] reactivity, and stereoselectivity.[25] Recent reports from these laboratories have disclosed several unique structural features of thiophosphonamide anions derived from **6a**, **7a**, and **8a**[24c,d] (Figure 1). In marked contrast to the solution structures observed in the corresponding phosphonamide anions (**6b**$^-$, **8b**$^-$),[24c,d] Li^+**6a**$^-$ and Li^+**8a**$^-$ displayed a striking dichotomy in their hybridization states. In solution, Li^+**6a**$^-$ and Li^+**8a**$^-$ exhibited the following characteristics: nearly planar sp^2 carbanionic carbons; solvent-separated ion pairs; monomeric structures. On the other hand, the spectroscopic studies of Li^+**7a**$^-$ support the existence of a lithium carbon contact in solution. In addition, an intriguing modulation of the hybridization of Li^+**7a**$^-$ from sp^3 to sp^2 was found upon changing the degree of lithium solvation by the addition of HMPA (4 equiv).

Inspired by these findings and the higher rotational barriers (9.1−11.4 kcal/mol) found in Li^+**8a**$^-$ compared to Li^+**8b**$^-$ (6.7−7.9 kcal/mol),[19] we sought to examine the significance of these factors on the alkylation behavior of chiral, P=S-stabilized carbanions.[24c] In addition, on the basis of highly diastereoselective alkylations of 2-benzyl-3-isopropyl-6-methyl-1,3,2-oxazaphosphorinane 2-oxide (Li^+(*cis*)-**9**$^-$),[25h] we have undertaken the alkylation studies of the *P*-ethyl and *P*-methoxymethyl analogs. Our ultimate goal in the design and development of chirally modified phosphorus reagents is to access either enantiomer of optically active alkylphosphonates with these three main α-substitution patterns by virtue of highly diastereoselective alkylation with appropriate phosphonamidate stereoisomers. We describe herein our endeavors toward this end by the employment of chiral thiophosphoryl-stabilized carbanionic reagents derived from (*S*)-*N*-isopropyl-4-amino-2-butanol.[25h]

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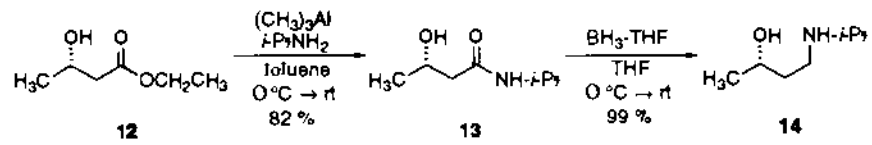
Scheme 3



The selection of *P*-(methoxymethyl)-1,3,2-oxazaphosphorinane 2-oxide **11** as the representative α-heteroatom-substituted phosphonate was based on several criteria. First, enantiomerically enriched α-hydroxyphosphonates have been shown to serve as biologically significant components (bioisosteres of α-hydroxy esters) in a peptidic framework for the synthesis of transition state analog inhibitors of proteolytic enzymes.[1e,f] Second, a variety of α-heteroatom-substituted phosphonates possessing potential biological activity can be readily synthesized by Mitsunobu[27] type transformation of the corresponding α-hydroxyphosphonates.[28] Third, despite their importance for the synthesis of enol ethers,[4,29] the alkylation of α-alkoxyphosphonates in a chiral environment has never been addressed.[30]

Results

Syntheses of Oxazaphosphorinane 2-Oxides 9−11 and 2-Sulfides 16−18. The preparation of (*S*)-*N*-isopropyl-4-amino-2-butanol (**14**) from ethyl (*S*)-3-hydroxybutyrate (**12**)[31] was carried out by a sequence of reactions similar to that employed in the synthesis of the corresponding *N*-*tert*-butyl analog[25b] (Scheme 3). Treatment of **12** with in-situ-prepared trimethylaluminum *N*-isopropylamide[32] in toluene at ambient temperature afforded 3-hydroxybutyramide (**13**) in 82% yield. The enantiomeric excess of **13** after recrystallization was determined to be 99.6% by HPLC analysis of the corresponding 3,5-dinitrophenyl carbamate derivative.[33] Borane reduction of the amide **13** at room temperature produced 1,3-amino alcohol **14** in essentially quantitative yield after distillation.

The oxazaphosphorinane 2-oxides, (6*S*)-(*u*)-**9** (*cis*-**9**), (6*S*)-(*u*)-**10** (*cis*-**10**) and (6*S*)-(*l*)-**9** (*trans*-**9**), (6*S*)-(*l*)-**10** (*trans*-**10**), were synthesized by simultaneous addition of the appropriate alkylphosphonic dichloride[34] and (*S*)-*N*-isopropyl-4-amino-2-butanol (**14**) in the presence of triethylamine to afford the easily

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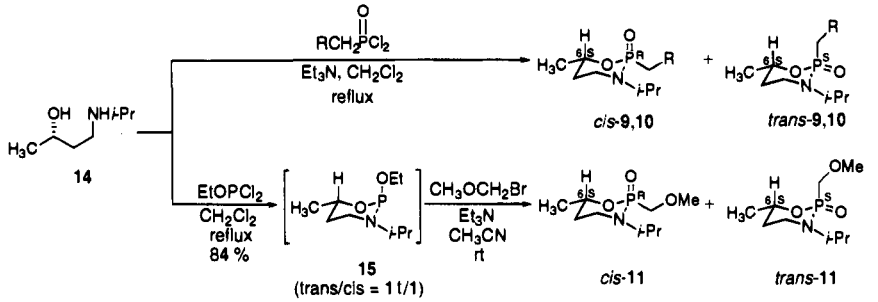
Table 1. Preparation of Substrates **9**−**11**



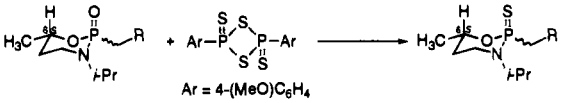
R	product	ratio (cis/trans)[a]	yield, % (cis/trans)	R	product	ratio (cis/trans)[a]	yield, % (cis/trans)
Ph	**9**	1.9/1	57/32	OMe	**11**	8.4/1	74/7
Me	**10**	1/1.2	42/46				

[a] Ratio determined by ^{31}P NMR.

separable diastereomers in good overall yields (89% (R = Ph), 88% (R = Me)) (Table 1).[35,36] The synthesis of **11** was performed by an alternative route involving the Arbuzov reaction[37] of phosphite **15** with bromomethyl methyl ether (MOMBr). The phosphite **15** (trans/cis, 11/1),[38] derived from the condensation of 1,3-amino alcohol **14** with ethyl dichlorophosphite in refluxing CH_2Cl_2 in 84% yield, was treated with MOMBr in CH_3CN at room temperature in the presence of triethylamine to provide *cis*-**11** and *trans*-**11** in a ratio of 8.4/1 and in 81% overall yield. It is important to note that the employed electrophile, MOMBr, is so reactive that the Arbuzov reaction can be performed under very mild conditions. In addition, an important feature associated with the role of triethylamine is that it serves as an HBr scavenger. Similar reaction conditions in the absence of triethylamine resulted in considerably lower yields due to the acid-catalyzed P−N bond cleavage. The stereostructures of **9**−**11** were assigned spectroscopically by analogy with the corresponding *N-tert*-butyl analog whose full stereostructure was confirmed by X-ray crystallographic analysis[25b] and by the diagnostic downfield shift of ^{31}P resonances in the *u* series.[39]

The enantiomerically enriched thiophosphonamidates **16**, **17**, and **18** were prepared by thiation of the corresponding phosphonamidates, **9**, **10**, and **11**, with Lawesson's reagent[40] in warm benzene (or toluene) to afford the easily purified, crystalline products in good yields (71−94%) (Table 2). In general, the cis stereoisomers are more susceptible to decomposition when the thiation reactions are conducted at elevated temperature and prolonged reaction time. The yield of *cis*-**17** dropped to 55% when the reaction was carried out at 110 °C. In addition, the unfavorable temperature effect became more severe in case of *cis*-**11**. Essentially complete decomposition of *cis*-**11** resulted when the transformation was performed at 110 °C. Thus, carefully monitoring the reaction progress by ^{31}P NMR spectroscopy was necessary to ensure the best thiation results. It is important to note that the thiation proceeded with complete retention of configuration at phosphorus as evidenced by ^{31}P NMR analysis of the crude reaction products and was ultimately secured by chemical correlation (*vide infra*).

Table 2. Preparation of Thiophosphonamidates **16**−**18**



R	solvent (*T*, °C)	product	yield, %
Ph (*cis*-**9**)	toluene (110)	*cis*-**16**	90
Ph (*trans*-**9**)	toluene (105)	*trans*-**16**	94
CH_3 (*cis*-**10**)	benzene (80)	*cis*-**17**	71
CH_3 (*trans*-**10**)	toluene (110)	*trans*-**17**	76
OCH_3 (*cis*-**11**)	toluene (80)	*cis*-**18**	79

The selected spectroscopic data and R_f values of phosphonamidates **9**−**11** and their 2-thioxo analogs are compiled in Table 3. Several important and informative features are noteworthy. First, a significant upfield shift in ^{31}P resonances was observed for R = Ph relative to R = Me. The chemical shift difference ($\Delta\delta$, negative numbers are upfield shifts) for phosphonamidates **9** and thiophosphonamidates **16** was about −8 ppm relative to the corresponding methyl-substituted analogs **10** and **17**. Even larger differences in chemical shift were observed for R = OMe compared to R = Me (−12 ppm (**11**) and −11 ppm (**18**)). The trend in the change in ^{31}P NMR chemical shifts seems consistent with the inductive effect associated with the R substituent.[41]

Second, the ^{31}P resonances of the cis stereoisomers were more downfield to a similar extent in both phosphonamidates **9**−**11** and thiophosphonamidates **16**−**18** as compared to those of the

(35) Yaun, C.; Li, S.; Cheng, Z. *Synthesis* **1988**, 186.

(36) The *like* (*l*) and *unlike* (*u*) nomenclature is used throughout to designate the configuration of the phosphorus and α-stereogenic centers with respect to (*S*)-C(6). See: Prelog, V.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. For reasons of simplicity (due to priority changes) and parallels between the phosphoryl and thiophosphoryl series, we designate the relative configuration between C(6) and P(2) as cis for HC(6)′ and XP(2) proximal and trans for HC(6) and XP(2) distal.

(37) (a) Bhattacharya, A. K.; Thygarajan, G. *Chem. Rev.* **1981**, *81*, 415. (b) Brill, T. S.; Landon, S. J. *Chem. Rev.* **1984**, *84*, 577.

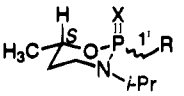
(38) (a) Huang, Y.; Mullah, N. N.; Sopchik, A. E.; Arif, A. M.; Bentrude, W. G. *Tetrahedron Lett.* **1991**, *32*, 899. (b) Hutchins, R. O.; Maryanoff, B. E.; Albrand, J. P.; Cogne, A.; Gagnaire, D.; Robert, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 9151. (c) Huang, Y.; Arif, A. M.; Bentrude, W. G. *J. Org. Chem.* **1993**, *58*, 6235. (d) Quin, L. D. *The Heterocyclic Chemistry of Phosphorus*; Wiley-Interscience: New York, 1981; p 196.

(39) (a) Gallagher, M. J. In *Methods in Stereochemical Analysis, Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis: Organic Compounds and Metal Complexes*; Verkade, J. G., Quin, L. D., Eds.; VCH Publishers Inc.: Deerfield, FL, 1987; Vol. 8, Chapter 9. (b) Spassov, S. L.; Lyapova, M. J.; Ivanova, M. E. *Phosphorus Sulfur Relat. Elem.* **1988**, *37*, 199. (c) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Chandrasekaran, S.; Ashby, M. T. *J. Am. Chem. Soc.* **1988**, *110*, 7119. (d) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Bajwa, G. S.; Burright, D. D.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6669. (e) Bajwa, G. S.; Chandrasekaran, S.; Hargis, J. H.; Sopchik, A. E.; Blatter, D.; Bentrude, W. G. *J. Am. Chem. Soc.* **1982**, *104*, 6385. (f) Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2083. (g) Harrison, J. M.; Inch, T. D.; Lewis, G. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1892. (h) Goodridge, R. J.; Hambley, T. W.; Ridley. D. D. *Aust. J. Chem.* **1986**, *39*, 591.

(40) (a) Horner, L.; Lindel, H. *Phosphorus Sulfur Relat. Elem.* **1982**, *12*, 259. (b) Kawashima, T.; Kojima, S.; Inamoto, N. *Chem. Lett.* **1989**, 849. (c) Shabana, R.; El-Kateb, A.; Osman, F. H. *Chem. Ind. (London)* **1984**, *6*, 552. (d) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

(41) Grim, S. O.; McFarlane, W.; Davidoff, E. F. *J. Org. Chem.* **1967**, *32*, 781.

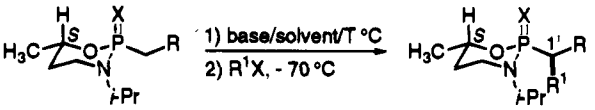
Table 3. Spectroscopic Data and R_f Values of Substrates **9**–**11** and Their 2-Oxide Analogs **16**–**18**



		X = O					X = S			
R	compd	δ^{31}P (ppm)[a]	δC(1′) (ppm)[b]	$^1J_{CP}$ (Hz)	R_f	compd	δ^{31}P (ppm)[c]	δC(1′) (ppm)[b]	$^1J_{CP}$ (Hz)	R_f[c]
Ph	*cis*-**9**	25.2	36.74	128.9	0.35[d]	*cis*-**16**	88.8	44.73	94.6	0.23
Ph	*trans*-**9**	22.6	34.15	119.6	0.50[d]	*trans*-**16**	84.4	39.44	83.9	0.30
Me	*cis*-**10**	33.2	20.62	135.2	0.28[e]	*cis*-**17**	95.8	28.83	100.7	0.25
Me	*trans*-**10**	30.1	17.98	123.4	0.48[e]	*trans*-**17**	92.5	23.48	90.0	0.20
OMe	*cis*-**11**	20.6	67.82	156.0	0.33[f]	*cis*-**18**	85.0	74.07	116.0	0.15
OMe	*trans*-**11**	17.8			0.43[f]					

[a] $CDCl_3$ at 121.6 or 162 MHz. [b] $CDCl_3$ at 75.5 or 100 MHz. [c] Benzene. [d] EtOAc/*i*-PrOH, 19/1. [e] Acetone/hexane, 5/1. [f] EtOAc/*i*-PrOH, 49/1.

Table 4. Alkylation with *cis*-Phosphonamidates *cis*-**9**–**11** and *cis*-Thiophosphonamidates *cis*-**16**–**18**



R	X	educt	conditions[a]	R¹X	product	ratio (1′*R*/1′*S*)[b]	yield,[c] %	δ_{major} ^{31}P, ppm	δ_{minor} ^{31}P, ppm	$\Delta\delta$[d]
Ph	O	*cis*-**9**[e]	A	MeI	**19**	33.8/1	93	29.1	28.2	0.9
	O	*cis*-**9**[e]	A	BnBr	**20**	16.5/1	89	27.9	25.6	2.3
	S	*cis*-**16**	A	MeI	**21**	>1000/1[f]	98.5	95.1	96.0	−0.9
	S	*cis*-**16**	A	BnBr	**22**	>1000/1[f]	93	94.25	94.40	−0.15
Me	O	*cis*-**10**	A	*n*-BuI	**23**	1/19.6[g]	94	34.94	35.01	−0.07
	O	*cis*-**10**	A	*i*-BuI	**24**	1/40[g]	87	35.37	35.58	−0.21
	O	*cis*-**10**	A	BnBr	**25**	1/19.6[g]	96	33.31	33.41	−0.1
	S	*cis*-**17**	B	*n*-BuI	**26**	1/15.6[g]	99.6	100.95	101.34	−0.39
	S	*cis*-**17**	C	*n*-BuI	**26**	1/6.1[g]	36[h]			
OMe	O	*cis*-**11**	A	MeI	**27**	2.25/1	92	23.1	24.4	−1.3
	O	*cis*-**11**	A	BnBr	**28**	3/1	99	21.72	23.74	−2.0
	S	*cis*-**18**	A	MeI	**29**	1/1.9	97[i]			
	S	*cis*-**18**	C	MeI	**29**	15.6/1	84.4	88.3	90.2	−1.9
	S	*cis*-**18**	D	MeI	**29**	1/11.1	93			

[a] A, *t*-BuLi/THF/−7.0 °C; B, *n*-BuLi/THF/−70 °C; C, *t*-BuLi/THF/−95 °C/HMPA (4.4 equiv); D, *t*-BuLi/Et_2O/−95 °C/PMDTA (1.2 equiv). [b] Determined by HPLC or ^{31}P NMR. [c] Isolated yield. [d] $\delta_{major} - \delta_{minor}$. [e] See ref 25h. [f] Signal to noise minimum. [g] Due to priority change. [h] *cis*-**17** was recovered in 55% yield. [i] Percent conversion based on ^{31}P NMR analysis.

corresponding trans stereoisomers. This observation has been, in general, deemed characteristic in various 1,3,2-dioxa- and 1,3,2-oxazaphosphorinanes[42] and may be explained in terms of favorable anomeric effect associated with those stereoisomers where the P=X bond is axially disposed in the heterocycle. This anomeric effect is manifested in the X-ray crystal structures of the corresponding *cis*-*N*-*tert*-butyl analogs and *cis*-2-(1-hydroxybenzyl)-*N*-isopropyl stereoisomers,[43] where a nearly planar nitrogen was observed only in the cis series.

Third, the ^{31}P resonance of the thiophosphonamidates **16**–**18** appeared significantly downfield compared to the 2-oxo counterparts ($\Delta\delta$ = 62–65 ppm). This phenomenon has been explained, in most instances, in terms of the decreasing pπ–dπ back-bonding in the 2-thioxo compounds.[44] However, in view of the experimental evidence in support of significant covalent character in the P=S bond stated previously, this difference in chemical shifts of thiophosphonamidates might also be rationalized by the increased polarizability of the sulfur atom. This rationale is also corroborated by the consistent downfield shifts of C(1′) in the thiophosphonamidates **16**–**18** as compared to those for the 2-oxo analogs due to their stronger deshielding anisotropic effect (Table 3), despite the fact that phosphonates are more electron-withdrawing substituents than the corresponding thiophosphonates.[45] The more electronegative nature associated with phosphonates is reflected in the significantly larger coupling constants $^1J_{CP}$ observed (120–156 Hz) in **9**–**11** relative to those (84–116 Hz) of the corresponding 2-thioxo counterparts **16**–**18**.

Fourth, with regard to TLC mobility the cis stereoisomers in the oxazaphosphorinane 2-oxides **9**–**11** are more polar than their *trans*-diastereomers (ΔR_f = 0.1–0.2). In marked contrast, there are small differences in mobility between *cis*- and *trans*-stereoisomers for the 2-sulfide analogs. In addition, the phosphonamidates **9**–**11** are significantly more polar than the corresponding 2-thioxo counterparts **16**–**18** due to the larger dipole associated with the P=O group.

Alkylation in the Cis Series. The alkylation studies were first carried out with the *cis*-thiophosphonamidates and comparisons with their P=O analogs were made by selecting the electrophiles that led to the least selective alkylations.[25h] As summarized in Table 4, the alkylation behavior of *cis*-1,3,2-oxazaphosphorinane 2-oxides *cis*-**9**, *cis*-**10**, and *cis*-**11** was found to be highly dependent on the nature of R substituents and electrophiles. For example, methylation of Li^+*cis*-$\mathbf{9}^-$ (R = Ph) proceeded with high selectivity (ds ≥ 16/1). The alkylation of

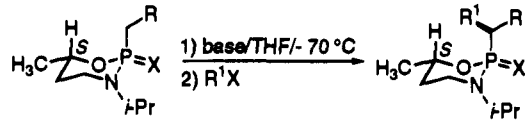
(42) (a) Majoral, J. P.; Navech, J. *Bull. Soc. Chim. Fr.* **1971**, 1331, 2609. (b) Inch, T. D.; Lewis, G. J. *J. Chem. Soc., Chem. Commun.* **1973**, 310. (c) Bentrude, W. G.; Tomasz, J. *Synthesis* **1984**, 27.

(43) (a) Dorow, R. L. Ph.D. Thesis, University of Illinois, 1990. (b) For the X-ray crystal structure of 2-(1-hydroxybenzyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-oxide, see: the supplementary material in Gordon, N. J.; Evans, S. A., Jr. *J. Org. Chem.* **1993**, *58*, 5293.

(44) (a) Postle, S. R. *Phosphorus Sulfur Relat. Elem.* **1977**, *3*, 269. (b) Schmidt, M. W.; Gordon M. S. *J. Am. Chem. Soc.* **1985**, *107*, 1922. (c) Cremer, S. E.; Cowles, J. M.; Farr, F. R.; Hwang, H.-O.; Kremer, P. W.; Peterson, A. C.; Gray, G. A. *J. Org. Chem.* **1992**, *57*, 511. (d) Liang, C.; Allen, L. C. *J. Am. Chem. Soc.* **1987**, *109*, 6449. (e) Albright, T. A.; Freeman, W. J.; Schweizer, E. E. *J. Org. Chem.* **1975**, *40*, 3437. (f) Davies, J. A.; Mierzwiak, J. G.; Syed, R. *J. Coord. Chem.* **1988**, *17*, 25.

(45) Modro, T. A. *Can. J. Chem.* **1977**, *55*, 3681 and references cited therein.

Table 5. Alkylations with *trans*-Phosphonamidates *trans*-**9** and *trans*-Thiophosphonamidates *trans*-**16** and *trans*-**17**



R	X	educt	base	R¹X	ratio (1′*S*/1′*R*)[a]	product	yield,[b] %	δ_{major} ^{31}P, ppm	δ_{minor} ^{31}P, ppm	$\Delta\delta$[c]
Ph	O	*trans*-**9**[d]	*t*-BuLi	MeI	5.8/1	**30**	100	27.44	27.86	−0.42
	O	*trans*-**9′**[e]	*t*-BuLi	BnBr	1.2/1	**31**	98		24.3	
	S	*trans*-**16**	*t*-BuLi	MeI	44.3/1	**32**	97	91.57	92.73	−1.16
	S	*trans*-**16**	*t*-BuLi	BnBr	15.6/1	**33**	95	89.07	90.16	−1.09
Me	S	*trans*-**17**	*n*-BuLi	*n*-BuI	1/12.6[f]	**34**	87[g]	97.65	98.00	−0.35

[a] Determined by HPLC or ^{31}P NMR analysis. [b] Isolated yield. [c] $\delta_{major} - \delta_{minor}$. [d] Reference 25h. [e] The *N*-*tert*-butyl analog was used (ref 25b). [f] Due to priority change. [g] About 12% of the starting material remained.

the *P*-ethyl anion Li$^+$*cis*-**10**$^-$ also proceeded smoothly to afford the products with high diastereomeric selectivity in a range of 19/1 (R^1 = *n*-Bu and Bn) to 40/1 (R^1 = *i*-Bu) and in good overall yield (87−96%). In marked contrast, the alkylation of Li$^+$*cis*-**11**$^-$ proceeded with surprisingly poor diastereoselectivity (2−3/1). Consistent with enolate alkylations where increasing the steric bulk of the electrophile leads to higher diastereoselection,[46] the alkylation of Li$^+$*cis*-**10**$^-$ with *i*-BuI provided the isobutylation products **24** in 87% with excellent diastereoselectivity (40/1). Despite the fact that benzylation (ds = 3/1) was only marginally more selective than the corresponding methylation (ds = 2.3/1), the alkylation profile of Li$^+$*cis*-**11**$^-$ likewise followed similar steric approach control. On the contrary, the methylation of Li$^+$*cis*-**9**$^-$ proceeded with higher selectivity (34/1) than that of the corresponding benzylation (17/1). This unusual behavior has been observed throughout the other four different *N*-substituted analogs.[25h]

The thiophosphoryl-stabilized anions were found to be excellent substrates to effect high asymmetric induction in alkylation reactions. The alkylation profile of thiophosphonamidates *cis*-**16**−**18** was also dependent on the group R and followed a similar trend as for the 2-oxo analogs. As illustrated in Table 4, the alkylation of thiophosphonamidate Li$^+$*cis*-**16**$^-$ proceeded with significantly higher diastereoselectivity than that of phosphonamidate Li$^+$*cis*-**9**$^-$.[47] A single diastereomer of the alkylation products was obtained in high yield (≥93%). In contrast to the alkylation behavior of the *P*-benzyl anions Li$^+$*cis*-**9**$^-$ and Li$^+$*cis*-**16**$^-$, butylation of *P*-ethylphosphonamidate Li$^+$*cis*-**10**$^-$ proceeded with slightly higher diastereoselection (20/1) as compared to the 2-thioxo counterpart Li$^+$*cis*-**17**$^-$ (16/1).[48] Further, conducting the butylation with Li$^+$*cis*-**17**$^-$ in the presence of HMPA (4.4 equiv) resulted in a significant decrease in reaction rate and diastereoselectivity (6.1/1).

The methylation of *P*-(methoxymethyl)thiophosphonamidate Li$^+$*cis*-**18**$^-$ was even more surprising. A poor but reversed diastereoselection (1/2) was observed when the reaction was conducted under the same reaction conditions as for Li$^+$*cis*-**11**$^-$. Interestingly, a significant improvement in diastereoselectivity (16/1) could be accomplished upon the addition of HMPA (4.4 equiv). Furthermore, the configuration at the newly created stereocenter in the major alkylation product was the same as that from Li$^+$*cis*-**11**$^-$ (*vide infra*). To our surprise, a reversal of diastereoselectivity to a similar extent (1/11.1) was observed when the methylation was performed in diethyl ether in the presence of PMDTA (1.2 equiv).[49]

Alkylation in the Trans Series. Considerable improvements in diastereoselective alkylation of the trans stereoisomers were observed by the employment of thiophosphoryl-stabilized carbanions (Table 5). The alkylation behavior of *trans*-phosphonamidates was also highly dependent on the steric and electronic demand of R substituents and electrophiles. The alkylation with Li$^+$*trans*-**16**$^-$ proceeded with uniformly higher selectivity (15∼44/1) than that of Li$^+$*trans*-**17**$^-$ (13/1) Table 5. Benzyl bromide remained the least selective electrophile in this study. The methylation of thiophosphonamidate Li$^+$*trans*-**16**$^-$ proceeded smoothly in 10 min to afford the methylation products (*l*)-**32** in high yield (97%) with excellent diastereoselectivity (44/1). However, only moderate diastereocontrol (6/1) resulted from the methylation with the corresponding 2-oxo counterpart Li$^+$*trans*-**9**$^-$. Similarly, a significant increase in the benzylation diastereoselection (15/1 vs 1.2/1) was accomplished by replacing phosphonamidate Li$^+$*trans*-**9′**$^-$ (*N*-*tert*-butyl analog) with thiophosphonamidate Li$^+$*trans*-**16**$^-$. Attempts to generalize the alkylation by the use of a secondary halide, i.e., 2-iodopropane, proved fruitless. Multicomponent product mixtures were obtained along with recovered *trans*-**16** (38%). This result is in accord with the increasing basicity of thiophosphoryl-stabilized carbanions.[20] Presumably, the competing E2 process becomes dominant under such circumstances. To test the influence of additives on lithium solvation, the butylation of Li$^+$*trans*-**17**$^-$ was conducted under similar reaction conditions in the presence of HMPA (4 equiv). While a single stereoisomer was isolated, the reaction proceeded sluggishly and less than 10% conversion was observed even after prolonged reaction time.

Epimerization Study and Chemical Shift Correlation. To secure the identity of the minor diastereomers derived from the highly diastereoselective alkylations, authentic samples were prepared by epimerization at the α-stereogenic center by employing a deprotonation−reprotonation protocol on the diastereomerically pure, major alkylation products (Table 6). Deprotonation of the major diastereomers was effected with *t*-BuLi in THF at −70 °C followed by warming to −20 °C. The resulting anions were quenched with a solution of acetic acid in THF to provide a mixture of diastereomers with significant enrichment (1/1−5/1) in the minor isomers not easily accessible by the previous alkylation studies. The identities of these minor diastereomers were unambiguously confirmed by spectroscopic correlation with the alkylation products and/or by full characterization of the isolated, purified materials.

We have also noted a relationship between the sense of asymmetric induction in the alkylation and the ^{31}P NMR

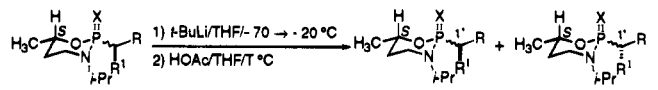
(46) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 1.

(47) The selectivities of >1000/1 in Table 4 represent conservative estimates based on the measured signal/noise ratio in the ^{31}P NMR spectra of these compounds (>9000/1 for **21**; >6500/1 for **22**). None of the minor products were detected.

(48) The diastereoselectivity difference between the benzylation of *P*-ethyloxazaphosphorinane 2-sulfide and 2-oxide was found to be even larger (11.5/1 vs 20/1).

(49) PMDTA: *penta*methyl*di*ethylene*tri*amine. A profound effect of PMDTA on the diastereoselective addition with the *P*-phenylthiomethyl analogue has been noted (ref 25i).

Table 6. Epimerization of Major Alkylation Products **19**–**25**



R	R^1	X	educt	*T*, °C	ratio (1′*R*/1′*S*)[a]	yield,[b] %
Ph	Me	O	(*u*)-**19**	−70	27/73	95
Ph	Bn	O	(*u*)-**20**	−70	53/47	87
Ph	Me	S	(*u*)-**21**	−20	17/83	98
Ph	Bn	S	(*u*)-**22**	−10	45/55	100
Me	*n*-Bu	O	(*u*)-**23**	−70	33/67	99
Me	*i*-Bu	O	(*u*)-**24**	−70	67/33	100
Me	Bn	O	(*u*)-**25**	−70	32/68	83
Ph	Me	S	(*l*)-**32**	−20	52/48	100

[a] Determined by HPLC or ^{31}P NMR. [b] Isolated overall yield.

chemical shifts of the alkylation products. Chemical shifts and chemical shift differences of the products from both the oxazaphosphorinane 2-oxides and 2-sulfides are included in Tables 4 and 5. In all cases except the products **19** and **20** derived from alkylation with Li^+*cis*-**9**$^-$, the ^{31}P NMR resonances of the major diastereomers are further upfield than those of the minor diastereomers. This observation also applies to all of the R^1 groups (electrophiles) surveyed. This trend suggests that the sense of asymmetric induction in the alkylation of thiophosphonamidates is the same as that produced in preponderance by the alkylation of the corresponding 2-oxo analogs.

Stereochemical Correlation. The stereochemical course of alkylations in the P=O and P=S series was unambiguously established by chemical correlation as outlined in Scheme 4. First, the stereochemical course of alkylation of *cis*-**9** and *cis*-**16** was shown to be the same by stereospecific, oxidative transformation of the major P=S methylation product (*u*)-**21** to the major P=O methylation product (*u*)-**19**. The absolute configuration at the newly created stereogenic center was thus found to be *R* in both cases by comparison of the optical rotations of dimethyl phosphonate (+)-**35** derived from both (*u*)-**19** and the corresponding *N-tert*-butyl analog, the configuration of which had previously been secured by X-ray crystallographic analysis.[25b,h] Thus, the electrophilic attack on both the *P*-benzylphosphonamidate *cis*-**9** and the 2-thioxo analog *cis*-**16** occurred preferentially from the *re* face of the derived anions. The absolute configurations of the alkylation products in the *P*-ethyl series (*cis*-**10** and *cis*-**17**) were then assigned to be *S* on the basis of the assumption that they both have the same facial preference in the electrophilic approach (*vide infra*).

The major alkylation products in the trans series were assigned in a similar fashion (Scheme 4). Treatment of (*l*)-**32** with mCPBA in CH_2Cl_2 at 0 °C afforded phosphonamidate (*l*)-**30** in 92% yield and likewise with complete stereospecificity. Hydrolytic cleavage of the heterocycle in the (*l*)-**30** with 6 N HCl at 110 °C followed by esterification of the intermediate phosphonic acid produced (−)-**35** indicating the *S* configuration. Thus, the electrophilic attack in both *P*-benzylphosphonamidate *trans*-**9** and the 2-thioxo analog *trans*-**16** proceeded with the same stereochemical preference, i.e., from the *si* face of the resulting anions. The configuration of the predominant butylation product in **34** (Table 5) was tentatively assigned to possess *R* configuration by analogy.

It is of interest to note that the stereochemical course of alkylation was controlled by the local asymmetric environment provided by the phosphorus stereogenic center. Since the oxidation of (*u*)-**21** and (*l*)-**32** with mCPBA proceeded smoothly at 0 °C to afford the corresponding phosphonamidates (*u*)-**19** and (*l*)-**30**, respectively, with complete retention of configuration[50] in quantitative yield, either enantiomer of dimethyl phosphonates in high optically purity can be obtained by taking advantage of the highly diastereoselective alkylation from the respective thiophosphonamidate stereoisomers.

To demonstrate the utility of *P*-(methoxymethyl)thiophosphonamidates for the synthesis of enantiomerically enriched α-hydroxyphosphonates and determine the stereochemical outcome in the methylation, a diastereomeric mixture (2.3/1) of the methylation products **27** was subjected to dealkylation reaction with TMSI[51] at ambient temperature followed by hydrolytic desilylation of the resulting silyl phosphonates and esterification (Scheme 5). Dimethyl (1-methoxyethyl)phosphonate **36** was obtained in 67% yield along with a small amount (19%) of (1-hydroxyethyl)phosphonate **37**, whose absolute configuration was assigned as *R* by comparison of the optical rotation of **37** with the literature values.[52a,b] Moreover, highly diastereomerically enriched (*u*)-**27** and (*l*)-**27** can be obtained in quantitative yield by independent oxidation of the 2-thioxo counterparts (*u*)-**29** and (*l*)-**29**.

These thioxo to oxo oxidative transformations again proceeded with complete retention of configuration at the phosphorus stereogenic center. In addition, the diastereomeric ratios of the oxidation products correspond well with those of the starting materials. While no epimerization of the C(1′) stereocenter occurred under the reaction conditions, the minor differences in *u*/*l* ratios must be due to loss of one diastereomer. In view of limited success for the synthesis of enantiomerically enriched α-hydroxyphosphonates reported in recent years,[52] the utilization of highly diastereoselective alkylation with Li^+(*l*)-**18**$^-$ by judicious choice of alkylation reaction conditions (solvents and additives) provides a useful synthesis of either antipode of dimethyl phosphonates **36** (or **37**) in high enantiomeric purity.

Discussion

Alkylation in the Cis Series. On the basis of X-ray crystallographic and spectroscopic studies of anions derived from **6**–**8**,[24] the stereochemical course of alkylation in the *P*-benzyl cis series can be rationalized in terms of the sp^2-

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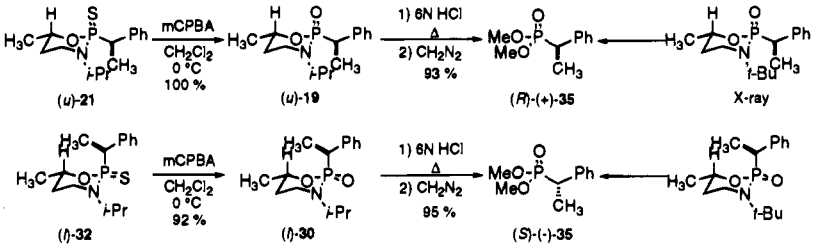
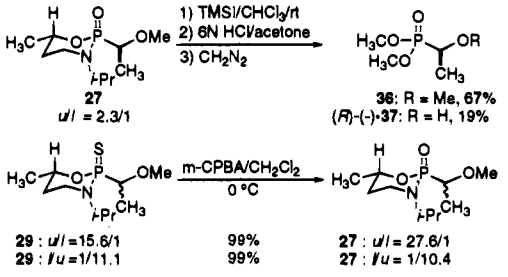
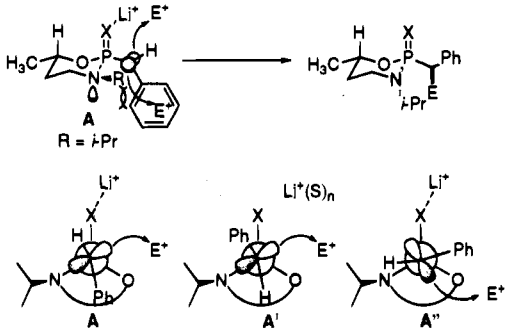
Scheme 4



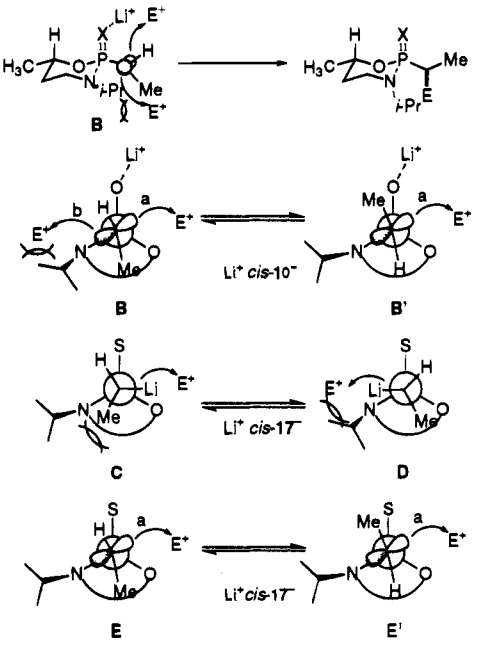
Scheme 5



Scheme 6



Scheme 7



hybridized anion in a reactive, parallel conformation **A** (Scheme 6). The conformer **A** preferentially adopts a chairlike conformation with the benzyl moiety in the equatorial position and the phenyl group in an antiparallel arrangement with the P=X group.[25h] Thus, the electrophile approaches predominantly to the side opposite to the nitrogen substituent (i.e., *i*-Pr) to avoid a severe nonbonding steric interaction. The dramatic increase in alkylation selectivity for the P=S substrate *cis*-**16** compared to the P=O substrate *cis*-**9** was striking. It is tempting to ascribe this change to the demonstrated increase in P—C rotational barrier for the P=S anions. However, the Curtin—Hammett principle dictates that we consider the population and reactivity of all conformers. Since the P=S anions are solvent-separated ions, an alternative parallel anion conformation **A'** would be less disfavored for Li^+*cis*-16^- than for the dimeric Li^+*cis*-9^- in which the lithium and THF groups provide a steric shield. This, however, would lead to the incorrect prediction of *decreased* selectivity for *cis*-**16**. We propose that the lower selectivity in *cis*-**9** arises from reaction through a different conformer **A''** (Scheme 6) which exposes the *si* face of the anion and would constitute a potential minimum.[18] The corresponding conformation in *cis*-**16** is expected to be much less energetically accessible due to poorer stabilization from the P—S σ orbital.[18]

The erosion of selectivity observed with *P*-ethylthiophosphonamidate Li^+*cis*-17^- indicates that the change in hybridization of the anions from sp^2 (Li^+*cis*-10^-) to sp^3 (Li^+*cis*-17^-) is a crucial factor in determining the stereochemical outcome.

This hypothesis can be better visualized by the Newman projections of the *P*-ethyl anions Li^+*cis*-10^- and Li^+*cis*-17^- (Scheme 7). For the sp^2-hybridized phosphoryl anion Li^+*cis*-10^-, the situation is analogous to that discussed above for Li^+*cis*-9^-. In the favored reactive conformation **B**, electrophilic attack occurs on the sterically more accessible face, path a. The similarity of benzylation selectivities for *cis*-**9** and *cis*-**10** suggest similar scenarios for this reaction pathway. The alternative parallel conformation **B'** is again disfavored due to methyl/lithium interactions.

For the sp^3-hybridized version (THF) of the thiophosphoryl anion Li^+*cis*-17^-, two limiting anion configurations must be considered (Scheme 7). In the anions **C** and **D** there are unfavorable nonbonding interactions between the methyl group (in **C**) or the incoming electrophile (in **D**) with the *N*-isopropyl group. Since these anions are most likely interconverting, their relative reactivity (not population) will determine the overall selectivity. Assuming a retentive S_E2 alkylation, it would appear that conformations related to **C** can explain the observed selectivity.

The addition of more than 4 equiv of HMPA presumably generates a solvent-separated ion pair which is now sp^2-hybridized,[24d] leading to the two limiting parallel conformations **E** and **E'** (Scheme 7). The erosion in selectivity compared to Li^+*cis*-10^- can be rationalized by competitive reaction via the minor parallel conformation **E'**, which should be less disfavored than **B'** due to the lack of an associated cation and its attendant solvent shell.

In contrast to the alkylation behavior of *P*-benzyl and *P*-ethyl anions Li^+*cis*-9^- and Li^+*cis*-10^-, the alkylation of the corresponding *P*-methoxymethyl analog Li^+*cis*-11^- would be expected to furnish products derived from the opposite orientation of the R group (OMe) due to chelation of Li^+ by the phosphoryl and methoxy oxygens (conformer **F**) (Scheme 8). As a consequence, the "opposite" face of the anion would undergo

Scheme 8

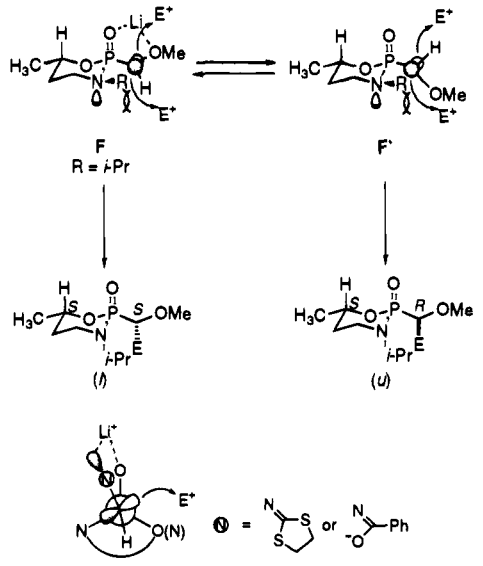


Figure 2. Proposed five-membered chelates in the anions with α-imino stabilizing groups.

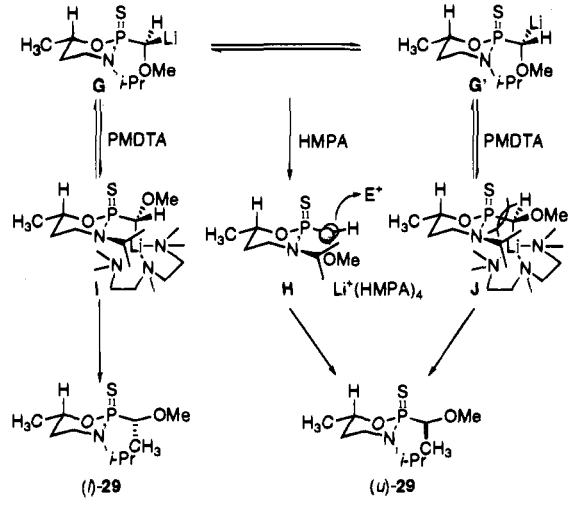
preferential electrophilic attack, leading to products with a reversal of configuration at the α-stereogenic center. However, as shown previously in Table 4, the alkylation of *P*-(methoxymethyl)phosphonamidate Li^+*cis*-**11**$^-$ led to the products with poor diastereoselectivity in ratios of 2.3~3/1 in favor of the *u* isomers.

One plausible explanation for this behavior is that the coordination of the methoxy oxygen to Li^+ is not strong enough to interrupt the coordination by solvent THF. Under such circumstances, the competing alkylation by way of the anion conformer **F'** similar to conformer **A** would result in erosion of selectivity and the observed stereochemical preference. Unfortunately, information concerning the preferred conformations and hybridization states of the phosphoryl- and thiophosphoryl-stabilized *P-alkoxymethyl* anions both in the solution and solid states is not available.

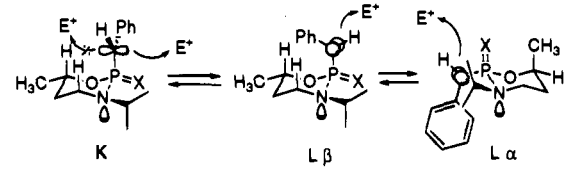
In marked contrast, five-membered chelates have been proposed in the highly diastereoselective alkylation of *P*-(iminomethyl)phosphonamides[10] and -phosphonamidates[11] where both coordination of the nitrogen lone pair to Li^+ (or K^+) and concomitant delocalization of the anionic charge into the C=N π^* orbital (Figure 2).

The reversal in diastereoselectivity of alkylation of Li^+*cis*-**18**$^-$ by modulation of lithium solvation is intriguing. On the basis of structure,[53] reactivity, and selectivity[54] of α-alkoxy carbanions, these observations can be understood in terms of two readily equilibrating sp^3-hybridized anions **G** and **G'** with carbon−lithium contacts[55] (Scheme 9). Complete solvation of

Scheme 9



Scheme 10



lithium ion by the addition of HMPA[24d,56] (≥4 equiv) would facilitate the formation of a planar anion **H**, where predominant electrophilic attack from the side syn to the ring oxygen would be expected to furnish (*u*)-**29**. On the other hand, the significant increase in steric bulk of the lithium upon tridentate coordination with PMDTA[57] can alter the conformational preferences of the intermediate anions **I** and **J**. Under such circumstances, the epimer **I** would be favored on the basis of steric considerations. Alkylation of **I** with retention of configuration[53,54] would afford (*l*)-**29** with the preferred *S* configuration at the newly created stereocenter.

Alkylation in the Trans Series. The alkylation behavior in the cis series, which exhibited significant improvement in alkylation diastereoselectivity by the utilization of thiophosphoryl-stabilized carbanions, strongly suggested that the unfavorable partitioning of reactive anionic conformers observed in Li^+*trans*-**9**$^-$ can be regulated by the use of the corresponding 2-thioxo analog Li^+ *trans*-**16**$^-$.

The size of the nitrogen substituent has a small effect on the stereochemical course of the alkylation in the trans series.[25h] Thus, the stereochemical outcome can be rationalized in terms of three competing reactive, anion conformers **K**, **Lα**, and **Lβ** (Scheme 10). In the case of oxazaphosphorinane 2-oxides (X=O), conformer **K** is most likely favored. Conformers **Lβ** and **Lα** are disfavored due to adverse steric interaction between

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(55) The configurational stability of α-alkoxy-stabilized anions can be significant reduced by incorporation of a vinyl or phenyl substituent. see: (a) Zschage, O.; Schwark; J.-R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 296. (b) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424. The rate of epimerization in diastereomeric α-phenylthio-stabilized carbanions has been shown to be highly dependent on the extent of lithium solvation. See: (c) McDougal, P. G.; Condon, B. D.; Laffosse, M. D., Jr.; Lauro, A. M.; VanDerveer, D. *Tetrahedron Lett.* **1988**, *29*, 2547.

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the phenyl group and axial hydrogens (in **Lβ**) or the methyl group and solvated OLi unit (**Lα**). Since the stereocontrol elements in **K** are the axial hydrogens, poor diastereoselection in the alkylation can be expected. In the corresponding thiophosphonamidate Li^+*trans*-**16**$^-$,[24c,d] the conformers **Lα** and **Lβ** maybe favored due to reduced 1,3-diaxial interaction, given the increase in the rotational barrier, elongated P=S bonds, and lack of cation coordination. Indeed, the separated ion pair nature of Li^+*trans*-**16**$^-$ may allow **Lα** in a twist boat version thereof to be favored.

Conclusion

The alkylation of 1,3,2-oxazaphosphorinane 2-sulfides proceeds with high selectivity in both cis and trans diastereomeric series. The enantiomerically enriched thiophosphonamidates of varying *P*-alkyl substitution were synthesized by thiation of the corresponding phosphonamidates with complete retention of configuration. The alkylation selectivity of *P*-benzylthiophosphonamidates was found to be significantly higher than that of the corresponding 2-oxo analogs. The alkylation selectivity of *P*-ethylthiophosphonamidates was attenuated in comparison to that observed in the corresponding 2-oxo analogs. This observation has been attributed to the hybridization and to the inherent selectivity difference between sp^3 and sp^2 anions. Highly enantioselective syntheses of α-hydroxyphosphonates in either antipodal form can be achieved by the employment of highly diastereoselective alkylation with anions derived from the corresponding *P*-methoxymethyl analog in the presence of HMPA or PMDTA.

The application of chiral thiophosphoryl-stabilized carbanions in asymmetric carbon−carbon bond-forming reactions offers significant synthetic promise. Their ease of preparation and highly stereospecific transformation to the corresponding phosphonamidates make them a useful alternative for electrophilic substitution reactions.

Experimental Section

^{1}H NMR spectra were recorded at 300 or 400 MHz, ^{13}C-NMR spectra at 100 or 75.5 MHz, and ^{31}P-NMR at 121.6 or 162 MHz in deuteriochloroform with tetramethylsilane (TMS) or chloroform as an internal reference unless otherwise stated. Phosphorus-31 spectra were referenced to external 85% H_3PO_4 (δ = 0.00 ppm). Chemical shifts are reported in ppm (δ): multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants are reported in hertz. In the carbon spectra all peaks for which a coupling constant is reported are doublets due to phosphorus coupling. Infrared spectra (IR) were recorded on an FT-IR spectrometer. Peaks are reported in cm^{-1} with the following relative intensities: s (strong 67−100%), m (medium 33−67%), or w (weak 0−33%). Electron impact (EI) mass spectra were obtained with ionization voltages of 70 or 10 eV, and high-resolution EI mass spectra were obtained with an ionization voltage of 70 eV. Data are reported in the form *m/z* (intensity relative to base peak = 100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Bulb-to-bulb distillations were performed with boiling points refer to air bath temperatures and were uncorrected. Melting points (mp) were uncorrected. Analytical TLC was performed on Merck SiO_2 plates with QF-254 indicator. Visualization was accomplished with UV light, iodine, and $KMnO_4$. Column (flash) chromatography was performed by the method of Still.[58] Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane, pentane, dichloromethane ($CaCl_2$); diethyl ether, *tert*-butyl methyl ether (TBME) ($CaSO_4$/$FeSO_4$); ethyl acetate (K_2CO_3). Solvents used for recrystallization were spectral grade and are given after the mp. Solvents used in reactions were reagent grade and were freshly distilled from the indicated drying agents: tetrahydrofuran (THF), sodium/benzophenone; benzene and toluene, CaH_2. Medium-pressure chromatography was performed using Merck Lobar columns. Analytical high-pressure liquid chromatography (HPLC) was performed with a spectrophotometric detector. The columns used were a Supelco LC-Si 5 μm column and Pirkle Covalent L-*N*-2-(naphthyl)alanine 5 μm column with the detector wavelength at 254 nm. The flow rate and solvent systems were as denoted. Retention times (t_R) and integrated ratios were obtained from an integrator. Optical rotations were reported as follows: $[\alpha]_{wavelength}$, solvent, and concentration (c = g/100 mL). *t*-BuLi was titrated according to the method of Gilman.[59] All reactions were run under an atmosphere of nitrogen.

(*S*)-*N*-(1-Methylethyl)-3-hydroxybutyramide (13). In an oven-dried, 100-mL, three-necked flask equipped with a thermometer, N_2 inlet, and septum was placed Me_3Al (4.7 mL, 48.4 mmol, 2.0 equiv) in anhydrous toluene (15 mL). A solution of isopropylamine (4.2 mL, 48.4 mmol, 2.0 equiv) in toluene (4 mL) was added dropwise to the reaction flask at 0 °C. The reaction mixture was stirred at 10 °C for 1 h and then warmed to room temperature (rt) for 50 min. The solution was cooled to 0 °C, and (*S*)-ethyl 3-hydroxybutanoate (3.199 g, 24.2 mmol) was added dropwise using a cannula (T < 0 °C). After 20 min, the reaction mixture was warmed to rt and stirred for 23 h. The reaction mixture was cooled to 0 °C, and H_2O (35 mL) was added cautiously. The mixture was acidified to *ca.* pH 6 with 6 N HCl and filtered through a Celite-packed sintered-glass to remove the aluminum salts. The aqueous layer was extracted with EtOAc (4 × 15 mL) followed by continuous extraction for 24 h. The combined organic layers were dried (K_2CO_3), filtered, and evaporated. The crude residue was purified by SiO_2 column chromatography (hexane/acetone, 3/2) to afford 2.878 g (82%) of **13** as a white solid. The enantiomeric purity of **13** was determined to be 99.6% by HPLC analysis of the corresponding 3,5-dinitrophenyl carbamate. An analytical sample was obtained by recrystallization from Et_2O/hexane: mp 61−62 °C (Et_2O/hexane); ^{1}H NMR (300 MHz) 6.03 (broad d, J = 2.2, 1H, NH), 4.18 (d, J = 3.1, 1H, OH), 4.15−4.11 (m, 1H, HC(3)), 4.09−4.00 (m, 1H, HC(1′)), 2.28 (dd, J_{gem} = 15.3, J_{vic} = 3.2, 1H, $H_aH_bC(2)$), 2.19 (dd, J_{gem} = 15.3, J_{vic} = 8.4, 1H, $H_aH_b(2)$), 1.17 (d, J = 6.2, 3H, $H_3C(4)$), 1.12 (d, J = 6.5, 6H, 2 × $H_3C(2')$); ^{13}C NMR (75.5 MHz) 171.5 C(1), 64.8 C(3), 43.8 C(2), 41.2 C(1′), 22.7 C(2′), 22.6 C(4); IR (CCl_4) 3300 (s), 1644 (s); MS (70 eV) 145 (M^+, 8), 44 (100); TLC R_f 0.13 (hexane/acetone, 2/1); HPLC t_R 9.94 min (*R*), 15.60 min (*S*) (Pirkle Covalent L-*N*-2-(naphthyl)alanine, hexane/*i*-PrOH, 94/6, 1.5 mL/min); $[\alpha]_D$ +44.19° (CH_2Cl_2, c = 0.57). Anal. Calcd for $C_7H_{15}NO_2$ (145.20): C, 57.90; H, 10.41; N, 9.65. Found: C, 58.06; H, 10.41; N, 9.62.

(*S*)-*N*-(1-Methylethyl)-4-amino-2-butanol (14). To a flame-dried, 250-mL, three-necked, flask equipped with an addition funnel, thermometer, stir bar, and N_2 inlet was introduced BH_3·THF (40.6 mL, 1.0 M in THF, 40.6 mmol, 3.05 equiv) at 0 °C. Hydroxy amide **13** (1.925 g, 13.3 mmol) in anhydrous THF (13.5 mL) was added dropwise through the addition funnel to the borane solution (T ~ 0 °C) over a period of 50 min. The solution was stirred at 0 °C for 2 h and warmed to rt for 26.5 h. The reaction mixture was cooled to 0 °C and carefully quenched by the addition of H_2O (1.7 mL) and HCl (6 N, 41 mL) to pH ~ 1. The mixture was stirred at rt for 7 h followed by addition of KOH pellets (about 23 g) at 0 °C to *ca.* pH 11. The organic layer was decanted, and the aqueous layer and salts were extracted with Et_2O (4 × 20 mL). A minimum amount of H_2O was added to dissolve the salts. The aqueous layer was continuously extracted with Et_2O for 24 h. The combined organic layers were dried (K_2CO_3), filtered, and evaporated. Kugelrohr distillation (80 °C, 10 Torr) of the residual liquid afforded 1.756 g (100%) of **14** as a colorless liquid: bp 85 °C (10 Torr, air bath); ^{1}H NMR (300 MHz) 3.96−3.86 (m, 1H, HC(2)), 2.95 (dt, J_{HH} = 11.9, J_{HH} = 3.9, 1H, $H_aH_bC(4)$), 2.75−2.61 (m, 2H, H_aH_bC-(4), HC(1′)), 1.59−1.52 (m, 1H, $H_aH_bC(3)$), 1.44−1.31 (m, 1H, H_aH_bC-(3)), 1.10 (d, J = 5.7, 3H, $H_3C(1)$), 1.00 (d, J = 6.3, 6H, 2 × $H_3C(2')$); ^{13}C NMR (75.5 MHz) 69.1 C(2), 48.4 C(1′), 45.7 C(4), 37.1 C(3), 23.4 C(1), 22.7 C(2′), 22.4 C(2′); IR (neat) 3276 (s), 2965 (s), 1472 (s); MS (70 eV) 131 (M^+, 13), 44 (100); TLC R_f 0.28 (acetone/hexane, 5/1); $[\alpha]_D$ −34.03° (CH_2Cl_2, c = 1.44). Anal. Calcd for $C_7H_{17}NO$ (132.22): C, 64.07; H, 13.06; N, 10.67. Found: C, 63.95; H, 13.06; N, 10.63.

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(*S*)-(2*u*,6*l*)-6-Methyl-3-(1-methylethyl)-2-(phenylmethyl)-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2*l*,6*l*)-6-Methyl-3-(1-methylethyl)-2-(phenylmethyl)-1,3,2-oxazaphosphorinane 2-Oxide (*cis*-9 and *trans*-9). Anhydrous Et_3N (1.8 mL, 12.8 mmol, 2.1 equiv) was added to refluxing CH_2Cl_2 (24 mL) in an oven-dried, 100-mL, three-necked flask equipped with a reflux condenser, N_2 inlet, stir bar, and septum. Amino alcohol **14** (799 mg, 6.097 mmol) and benzylphosphonic dichloride (1.34 g, 6.4 mmol, 1.05 equiv) were each dissolved in anhydrous CH_2Cl_2 (14 mL) under nitrogen. Each solution was introduced to a 10 mL gas-tight syringe and added dropwise using a syringe pump over a period of 3.5 h to the reaction flask. The reaction mixture was stirred at reflux for 1 h after the addition was complete and then stirred at rt for 11 h. Water (20 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (K_2CO_3), filtered, and evaporated. ^{31}P NMR spectroscopic analysis of crude products showed a ratio of 1.9/1 (*cis*/*trans*). The residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 19/1) to give 524 mg (32.2%) of *trans*-**9** and 927 mg (56.9%) of *cis*-**9**. Analytical samples were obtained by recrystallization from hexane and pentane, respectively. Data for *trans*-**9**: mp 74−75 °C (hexane); ^1H NMR (300 MHz) 7.31−7.19 (m, 5H, Ph), 4.20−4.11 (m, 1H, HC(6)), 3.89−3.77 (m, 1H, $(CH_3)_2CHN$), 3.23 (dd, J_{HP} = 19.9, J_{HH} = 15.2, 1H, $H_aH_bC(1')$), 3.14−3.02 (m, 1H, $H_{eq}C(4)$), 2.89−2.79 (m, 1H, $H_{ax}C(4)$), 1.74−1.57(m, 2H, $H_2C(5)$), 1.31 (dd, J_{HP} = 6.1, J_{HH} = 1.1 , 3H, $H_3C(7)$), 1.13 (d, J = 6.6, 3H, $H_3C(9)$), 0.88 (d, J = 6.8, 3H, $H_3C(9)$); ^{13}C NMR (75.5 MHz) 132.9 (J = 8.1, C_{ipso}), 129.6 (J = 6.0, C_{ortho}), 128.4 (J = 2.5, C_{para}), 126.4 (J = 3.2, C_{meta}), 77.2 (J = 8.2, C(6)), 46.0 (J = 3.8, $(CH_3)_2CHN$), 38.1 (J = 2.4, C(4)), 34.2 (J = 119.6, C(1′)), 34.0 (J = 6.2, C(5)), 22.5 (J = 6.4, C(7)), 21.4 (C(9)), 20.0 (J = 3.4, C(9′)); ^{31}P NMR (121.65 MHz) 22.63; lR ($CDCl_3$) 3081 (w), 2977 (m), 1248 (s, P=O); MS (70 eV) 267 (M^+, 9), 252 (100); TLC R_f 0.5 (EtOAc/*i*-PrOH, 19/1); HPLC t_R 8.25 min (Supelco LC-Si, hexane/2-propanol, 24/1, 1 mL/min); $[\alpha]_D$ −46.9° (CH_2Cl_2, c = 1.3). Anal. Calcd for $C_{14}H_{22}NO_2P$ (267.30): C, 62.90; H, 8.30; N, 5.24; P, 11.59. Found: C, 62.98; H, 8.30; N, 5.28; P, 11.67. Data for *cis*-**9**: mp 58−59 °C (pentane); ^1H NMR (300 MHz) 7.32−7.15 (m, 5H, Ph), 4.44−4.34 (m, 1H, HC(6)), 3.92−3.80 (m, 1H, $(CH_3)_2CHN$), 3.23 (dd, J_{HP} = 18.9, J_{HH} = 15.0, 1H, $H_aH_bC(1')$), 3.16 (dd, J_{HP} = 17.0, J_{HH} = 15.0, 1H, $H_aH_bC(1')$, 3.01−2.89 (m, 1H, $H_{ax}C(4)$), 2.73−2.63 (m, 1H, $H_{eq}C(4)$), 1.61−1.56 (m, 1H, $H_{eq}C(5)$), 1.23 (d, J = 6.6, 3H, $H_3C(9)$), 1.20 (dd, J_{HH} = 6.1, J_{HP} = 1.2, 3H, $H_3C(7)$), 1.09 (d, J = 6.8, 3H, $H_3C(9)$), 0.97−0.74 (m, 1H, $H_{ax}C(5)$); ^{13}C NMR (75.5 MHz) 133.6 (J = 9.5, C_{ipso}), 129.8 (J = 5.9, C_{ortho}), 128.1 (J = 3.1, C_{para}), 126.3 (J = 3.6, C_{meta}), 72.8 (J = 8.1, C(6)), 46.3 (J = 4.6, $(CH_3)_2CHN$), 37.1 C(4), 36.7 (J = 128.9, C(1′)), 32.1 (J = 3.7, C(5)), 21.9 (J = 8.3, C(7)), 20.9 (C(9)), 20.2 (J = 5.3, C(9′)); ^{31}P NMR (121.65 MHz) 25.20; IR ($CDCl_3$) 3031 (w), 2975 (m), 1264 (s, P=O); MS (70 eV) 267 (M^+, 3), 252 (100); TLC R_f 0.35 (EtOAc/*i*-PrOH, 19/1); HPLC t_R 8.33 min (Supelco LC-Si, EtOAc/*i*-PrOH, 9/1, 1.0 mL/min); $[\alpha]_D$ +29.2° (CH_2Cl_2, c = 0.47). Anal. Calcd for $C_{14}H_{22}NO_2P$ (267.30): C, 62.90; H, 8.30; N, 5.24; P, 11.59. Found: C, 62.84; H, 8.32; N, 5.29; P, 11.47.

(*S*)-(2*u*,6*l*)-2-Ethyl-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2*l*,6*l*)-2-Ethyl-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide (*cis*-10 and *trans*-10). Anhydrous Et_3N (1.2 mL, 8.63 mmol, 2.1 equiv) and anhydrous CH_2Cl_2 (22 mL) were introduced to an oven-dried, 100-mL, three-necked, round-bottomed flask equipped with a reflux condenser topped with a N_2 inlet, glass stopper, and septum. The solution was heated to gentle reflux. (*S*)-*N*-Isopropyl-4-amino-2-butanol (**14**) (539 mg, 4.11 mmol) and ethylphosphonic dichloride (461 μL, 4.31 mmol, 1.05 equiv) were each dissolved in anhydrous CH_2Cl_2 (5 mL) under nitrogen. Each solution was introduced to a 5-mL gas-tight syringe and added dropwise using a syringe pump over 3 h. The reaction mixture was heated to reflux for 3 h after the addition was complete and stirred at rt for 2.5 h. H_2O (15 mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (5 × 30 mL). The combined extracts were dried (K_2CO_3), filtered, and evaporated. The residual yellow oil was purified by silica gel column chromatography (acetone/hexane, 5/1) to give 384 mg (45.5%) of *trans*-**10** and 358 mg (42%) of *cis*-**10**. Analytical samples were obtained by Kugelrohr distillation. Data from *trans*-**10**: bp 70 °C (0.1 Torr, air bath); ^1H NMR (300 MHz) 4.25−4.18 (m, 1H, HC(6)), 3.95−3.83 (m, 1H, $(H_3C)_2CHN$), 3.18- 3.04 (ddt, J = 17.0, 13.0, 4.0, 1H, $H_{eq}C(4)$), 2.95−2.86 (m, 1H, $H_{ax}C(4)$), 1.81−1.60 (m, 4H, $H_2C(5)$, $H_2C(1')$), 1.31 (d, J = 6.3, 3H, $H_3C(7)$), 1.10 (dt, J_{HP} = 19.0, J_{HH} = 7.5, 3H, $H_3C(2')$), 1.11 (d, J = 6.8, 3H, $H_3C(9_a)$), 1.0 (d, J = 6.7, 3H, $H_3C(9_b)$); ^{13}C NMR (75.5 MHz) 75.3 (J = 7.4, C(6)), 45.4 (J = 4.1, $(H_3C)_2CHN$), 38.0 (J = 2.6, C(4)), 34.2 (J = 5.4, C(5)), 22.6 (J =7.0, $H_3CC(6)$), 21.2 ($C(9_a)$), 20.3 (J = 2.6, $C(9_b)$), 18.0 (J = 123.4, C(1′)), 6.6 (J = 2.6, C(2′)); ^{31}P NMR (121.65 MHz) 30.06; IR (CCl_4) 2975 (s), 1225 (s); MS (70 eV) 205 (M^+, 7), 190 (100); TLC R_f 0.48 (acetone/hexane, 5/1); $[\alpha]_D$ −88.09° (CH_2Cl_2, c = 1.39). Anal. Calcd for $C_9H_{20}NO_2P$ (205.23): C, 52.67; H, 9.82; N, 6.82; P, 15.09. Found: C, 52.58; H, 9.83; N, 6.82; P, 15.12. Data from *cis*-**10**: bp 60 °C (0.1 Torr, air bath); ^1H NMR (300 MHz) 4.49−4.39 (m, 1H, HC(6)), 3.70−3.58 (m, 1H, $(H_3C)_2CHN$), 3.12−2.97 (ddd, J = 16.3, 11.0, 5.4, 1H, $H_{ax}C(4)$), 2.97−2.87 (ddt, J = 16.3, 11.0, 5.1, 1H, $H_{eq}C(4)$), 1.87−1.82 (m, 1H, $H_{eq}C(5)$), 1.71 (dq, J_{HP} = 15.4, J_{HH} = 7.8, 2H, $H_2C(1')$), 1.67−1.54 (m, 1H, $H_{ax}C(5)$), 1.24 (d, J = 6.3, 3H, $H_3C(7)$), 1.16 (d, J = 6.6, 3H, $H_3C(9_a)$), 1.05 (d, J = 6.6, 3H, $H_3C(9_b)$), 1.02 (dt, J_{HP} = 19.4, J_{HH} = 7.5, 3H, $H_3C(2')$); ^{13}C NMR (75.5 MHz) 71.5 (J = 7.4, C(6)), 45.8 (J = 4.5, $(H_3C)_2CHN$), 36.8 (C(4)), 33.2 (J = 3.1, C(5)), 22.1 (J = 8.2, $H_3CC(6)$), 20.6 (J = 135.2, C(1′)), 20.4 (J = 6.1, $C(9_a)$), 20.2 ($C(9_b)$), 7.3 (J = 7.0, C(2′)); ^{31}P NMR (121.65 MHz) 33.17; IR (CCl_4) 2971 (s), 1217 (s); MS (70 eV) 205 (M^+, 9), 190 (100); TLC R_f 0.28 (acetone/hexane, 5/1); $[\alpha]_D$ +10.12° (CH_2Cl_2, c = 0.81). Anal. Calcd for $C_9H_{20}NO_2P$ (205.23): C, 52.67; H, 9.82; N, 6.82; P, 15.09. Found: C, 52.63; H, 9.86; N, 6.86; P, 15.21.

(*S*)-(2*u*,6*l*)-2-(Methoxymethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide (*cis*-11). In an oven-dried 250-mL, three-necked round-bottomed flask fitted with a reflux condenser topped with a N_2 inlet, glass stopper, and septum was introduced anhydrous CH_2Cl_2 (35 mL). Freshly distilled ethyl dichlorophosphite (630 μL, 5.51 mmol, 1.05 equiv) was added followed by addition of anhydrous Et_3N (1.61 mL, 11.56 mmol, 2.2 equiv) with generation of white smoke. The resulting mixture was heated to gentle reflux, and a solution of (*S*)-*N*-isopropyl-4-amino-2-butanol (**14**) (689 mg, 5.25 mmol) in anhydrous CH_2Cl_2 (14 mL) was added dropwise over a period of 25 min. The reaction mixture was stirred at reflux for 12 h. After having been cooled to rt, the mixture was added anhydrous hexane (140 mL) with precipitation of white solids. The solution was filtered through a Schlenk tube and the solvent removed under reduced pressure. The residual oil was purified by Kugelrohr distillation (90 °C, 10 Torr) to give the intermediate phosphite **15** (906 mg, 84%) as a colorless liquid. ^{31}P NMR spectroscopic analysis showed a diastereomeric ratio of 10.7/1 (trans/cis).

A solution of the phosphite **15** (447 mg, 2.18 mmol) in anhydrous CH_3CN (10 mL) was introduced to an oven-dried, 25-mL, three-necked, round-bottomed flask equipped with a N_2 inlet, glass stopper, and septum in the presence of the molecular sieves 4 Å (0.25 g). Methyl bromomethyl ether (320 μL, 3.92 mmol, 1.8 equiv) was added over 1 min followed by addition of anhydrous Et_3N (304 μL, 2.18 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 18 h and then passed through a short plug of Celite to remove the molecular sieves. The filtrate was immediately quenched with 10% aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 40 mL), and the combined organic extracts were dried (K_2CO_3), filtered, and concentrated under reduced pressure to afford a yellow oil. The residual oil was analyzed by ^{31}P NMR spectroscopy which showed a ratio of 8.4/1 (cis/trans). The residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 49/1) to yield 356 mg (74%) of *cis*-**11** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation: bp 80 °C (0.1 Torr, air bath); ^1H NMR (300 MHz) 4.48−4.40 (m, 1H, HC(6)), 3.87−3.75 (m, 1H, $(CH_3)_2CHN$), 3.58 (dd, J = 7.5, 1.4, 2H, $H_2C(1')$), 3.34 (d, J = 1.0, 3H, H_3CO), 3.06−2.98 (m, 2H, $H_2C(4)$), 1.87−1.74 (m, 2H, $H_2C(5)$), 1.26 (dd, J = 6.2, 1.4, $CH_3C(6)$), 1.16 (dd, J = 6.7, 1.2, 3H, $(H_3C)_a(H_3C)_bCHN$), 1.07 (dd, J = 6.8, 1.2, 3H, $(H_3C)_a(H_3C)_bCHN$); ^{13}C NMR (75.5 MHz) 73.6 (J = 8.0, C(6)), 67.8 (J = 156.0, C(1′)), 60.8 (J = 14.5, OCH_3), 45.8 (J = 5.0, $(H_3C)_2CHN$), 37.3 (C(4)), 32.5 (J = 4.5, C(5)), 22.1 (J = 7.3, $CH_3C(6)$), 20.7 ($(H_3C)_a(H_3C)_bCHN$), 20.2 (J = 2.9, $(H_3C)_a(H_3C)_bCHN$); ^{31}P NMR (121.65 MHz) 20.61; IR (CCl_4) 2975 (s), 1228 (s); MS (70 eV) 221 (M^+, 5), 206 (100); TLC R_f 0.33 (EtOAc/*i*-PrOH, 49/1); $[\alpha]_D$ +2.74°

(CH_2Cl_2, $c = 0.59$). Anal. Calcd for $C_9H_{20}NO_3P$ (221.23): C, 48.86; H, 9.11; N, 6.33; P, 14.00. Found: C, 48.66; H, 9.28; N, 6.22; P, 13.80.

(*S*)-(2*l*,6*l*)-6-Methyl-3-(1-methylethyl)-2-(phenylmethyl)-1,3,2-oxazaphosphorinane 2-Sulfide (*cis*-16). General Procedure. In a flame-dried, 25-mL, three-necked, round-bottomed, flask equipped with a glass stopper, reflux condenser, and septum was placed Lawesson's reagent (338 mg, 0.835 mmol, 1.04 equiv). A solution of *cis*-**9** (429 mg, 1.605 mmol) in anhydrous toluene (7 mL) was added using a cannula. The resulting heterogeneous mixture was stirred at 110 °C and became homogeneous in 3 min. The reaction was complete in 3 h as judged by ^{31}P NMR spectroscopic analysis of a crude, concentrated aliquot. The reaction mixture was cooled to rt and quenched with aqueous $NaHCO_3$ (9 mL, saturated $NaHCO_3/H_2O$ 7/2). The aqueous layer was separated and extracted with benzene (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give a yellowish oil. The oil was purified by SiO_2 column chromatography (benzene) to give 408 mg (90%) of *cis*-**16** as a white solid. An analytical sample was obtained by recrystallization from pentane: mp 48−49.5 °C (pentane); ^1H NMR (300 MHz) 7.33−7.22 (m, 5H, Ph), 4.58−4.50 (m, 1H, HC(6)), 3.72 (dm, $J_{HP} = 13.2$, $J_{HH} = 6.6$, 1H, $(CH_3)_2CHN$), 3.54 (dd, $J_{HP} = 25.7$, $J_{HH} = 15.0$, 1H, $H_aH_bC(1')$), 3.49 (dd, $J_{HP} = 22.8$, $J_{HH} = 15.0$, $H_aH_bC(1')$), 3.09−2.97 (m, 1H, $H_{ax}C(4)$), 2.74 (ddt, $J_{HP} = 17.4$, $J_{HH} = 12.1$, 4.9, 1H, $H_{eq}C(4)$), 1.77−1.68 (m, 1H, $H_{eq}C(5)$), 1.42−1.30 (m, 1H, $H_{ax}C(5)$), 1.29 (dd, $J_{HH} = 6.2$, $J_{HP} = 1.5$, 3H, $CH_3C(6)$), 1.19 ($J = 6.6$, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.93 ($J = 6.7$, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (75.5 MHz) 132.5 ($J = 10.1$, C_{ipso}), 130.0 ($J = 6.0$, C_{ortho}), 128.0 ($J = 3.0$, C_{para}), 126.7 ($J = 3.6$, C_{meta}), 71.0 ($J = 7.3$, C(6)), 47.3 ($J = 5.0$, $(CH_3)_2CHN$), 44.7 ($J = 94.6$, C(1')), 36.7 (C(4)), 33.7 ($J = 2.1$, C(5)), 22.2 ($J = 9.3$, $CH_3C(6)$), 20.7 ($J = 8.3$, $(CH_3)_a(CH_3)_bCHN$), 18.8 ($(CH_3)_a(CH_3)_bCHN$); ^{31}P NMR (161.9 MHz) 88.79; IR ($CHCl_3$) 3022 (m), 2976 (s), 1227 (m); MS (70 eV) 283 (M^+, 5), 192 (100); TLC R_f 0.23 (benzene); $[\alpha]_D$ +36.9° ($CHCl_3$, $c = 0.58$). Anal. Calcd for $C_{14}H_{22}NOPS$ (283.37): C, 59.34; H, 7.83; N, 4.94; P, 10.93; S, 11.31. Found: C, 59.36; H, 7.84; N, 5.00; P, 10.85; S, 11.22.

(*S*)-(2*u*,6*l*)-6-Methyl-3-(1-methylethyl)-2-(phenylmethyl)-1,3,2-oxazaphosphorinane 2-Sulfide (*trans*-16). By following the general procedure, from Lawesson's reagent (560 mg, 1.38 mmol, 1 equiv) and *trans*-**9** (740 mg, 27.66 mmol) in anhydrous toluene (11 mL) after heating at 110 °C for 14 h was obtained the crude thiophosphonamidate as a yellowish oil. The residual oil was purified by SiO_2 column chromatography (benzene) to give 734 mg (93.6%) of *trans*-**16** as a white solid. An analytical sample was obtained by recrystallization from hexane: mp 76−77 °C (hexane); ^1H NMR (400 MHz) 7.35−7.22 (m, CH, Ph), 4.45−4.37 (m, 1H, HC((6)), 4.20 (dsept, $J_{HP} = 13.4$, $J_{HH} = 6.7$, 1H, $(CH_3)_2CHN$), 3.44 (d, $J_{HP} = 16.1$, 2H, $H_2C(1')$), 3.23 (ddt, $J_{HP} = 23.7$, $J_{HH} = 13.7$, 4.2, 1H, $H_{eq}C(4)$), 3.10−3.02 (m, 1H, $H_{ax}C(4)$), 1.77−1.66 (m, 2H, $H_2C(5)$), 1.37 (dd, $J_{HH} = 6.1$, $J_{HP} = 1.1$, 3H, $H_3CC(6)$), 1.10 (d, $J = 6.6$, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.83 (d, $J = 6.6$, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (100 MHz) 132.6 ($J = 8.4$, C_{ipso}), 129.9 ($J = 5.3$, C_{ortho}), 128.1 ($J = 3.1$ C_{para}), 126.6 ($J = 3.8$, C_{meta}), 76.1 ($J = 9.2$, C(6)), 47.7 ($J = 5.3$, $(CH_3)_2CHN$), 39.4 ($J = 83.9$, C(1')), 38.2 (C(4)), 34.4 ($J = 5.3$, C(5)), 22.9 ($J = 7.6$, $CH_3C(6)$), 21.2 ($J = 2.3$, $(CH_3)_a(CH_3)_bCHN$), 20.0 ($J = 3.8$, $(CH_3)_a(CH_3)_bCHN$); ^{31}P NMR (161.9 MHz) 84.39; IR (CCl_4) 2975 (m), 1175 (s); MS (70 eV) 283 (M^+, 25), 192 (100); TLC R_f 0.30 (benzene); $[\alpha]_D$ −90.4° (CH_2Cl_2, $c = 0.25$). Anal. Calcd for $C_{14}H_{22}NOPS$ (283.37): C, 59.34; H, 7.83; N, 4.94; P, 10.93; S, 11.31. Found: C, 59.36; H, 7.86; N, 4.92; P, 10.87; S, 11.25.

(*S*)-(2*l*,6*l*)-2-Ethyl-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide (*cis*-17). By following the general procedure, from Lawesson's reagent (966 mg, 2.39 mmol, 1.06 equiv) and *cis*-**10** (925 mg, 4.51 mmol) in anhydrous benzene (18 mL) after heating at reflux for 3 h and 50 min was obtained the crude thiophosphonamidate as a yellowish oil. The residual oil was purified by SiO_2 column chromatography (benzene) to give 711 mg (71%) of *cis*-**17** as a white solid. An analytical sample was obtained by recrystallization from pentane: mp 57−58 °C (pentane); ^1H NMR (400 MHz) 4.65−4.55 (m, 1H, HC(6)), 3.53 (dsept, $J_{HP} = 13.2$, $J_{HH} = 6.6$, 1H, $(CH_3)_2CHN$), 3.13 (ddt, $J_{HH} = 11.2$, $J_{HP} = 7.1$, $J_{HH} = 3.9$, 1H, $H_{ax}C(4)$), 2.93 (ddt, $J_{HP} = 22.5$, $J_{HH} = 12.0$, 4.2, $H_{eq}C(4)$), 2.16−1.98 (m, 2H,CH_2CH_3), 1.85−1.78 (m, 1H, $H_{eq}C(5)$), 1.68 (ddt, $J = 13.7$, 11.0, 4.9, 1H, $H_{ax}C(5)$), 1.30 (dd, $J_{HH} = 6.1$, $J_{HP} = 1.2$, 3H, $H_3CC(6)$), 1.20 (d, $J = 6.6$, 3H, $(CH_3)_a(CH_3)_bCHN$), 1.15 (dt, $J_{HP} = 20.8$, $J_{HH} = 7.6$, 3H, CH_2CH_3), 1.08 (d, $J = 6.8$, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (100 MHz) 70.5 ($J = 6.9$, C(6)), 47.0 ($J = 4.6$, $(CH_3)_2CHN$), 36.8 (C(4)), 34.3 ($J = 2.3$, C(5)), 28.8 ($J = 100.71$, CH_2CH_3), 22.2 ($J = 9.2$, $CH_3C(6)$), 21.2 ($J = 9.2$, $(CH_3)_a(CH_3)_bCHN$), 18.0 ($(CH_3)_a(CH_3)_bCHN$), 7.2 ($J = 6.9$, CH_2CH_3); ^{31}P NMR (161.9 MHz) 95.77; IR (CCl_4) 2973 (s), 1169 (s); MS (70 eV) 222 (M + 1^+, 12), 221 (M^+, 100); TLC R_f 0.25 (benzene); $[\alpha]_D$ +33.2° (CH_2Cl_2, $c = 0.30$). Anal. Calcd for $C_9H_{20}NOPS$ (221.30): C, 48.85; H, 9.11; N, 6.33; P, 14.00; S, 14.49. Found: C, 48.76; H, 9.09; N, 6.32; P, 13.95; S, 14.45.

(*S*)-(2*u*,6*l*)-2-Ethyl-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide (*trans*-17). By following the general procedure, from Lawesson's reagent (815 mg, 2.01 mmol, 1.06 equiv) and *trans*-**10** (780 mg, 3.8 mmol) in anhydrous toluene (15.2 mL) after heating at 110 °C for 3 h was obtained the crude thiophosphonamidate as a yellowish oil. The residual oil was purified by SiO_2 column chromatography (benzene) to give 638 mg (75.8%) of *trans*-**17** as a white solid. An analytical sample was obtained by recrystallization from pentane: mp 46−47 °C (pentane); ^1H NMR (400 MHz) 4.33 (dsept, $J_{HP} = 13.4$, $J_{HH} = 6.8$, 1H, $(CH_3)_2CHN$), 4.32−4.22 (m, 1H, HC(6)), 3.21 (ddt, $J_{HP} = 21.0$, $J_{HH} = 13.7$, 3.9, 1H, $H_{eq}C(4)$), 3.06−2.94 (m, 1H, $H_{ax}C(4)$), 2.12 (ddq, $J_{HP} = 15.1$, $J_{HH} = 15.1$, 7.6, 1H, $H_aH_bCCH_3$), 1.87 (ddq, $J_{HH} = 15.1$, $J_{HP} = 12.5$, $J_{HH} = 7.6$, 1H, $H_aH_bCCH_3$), 1.74−1.65 (m, 2H, $H_2C(5)$), 1.35 (dd, $J_{HH} = 6.1$, $J_{HP} = 1.7$, 3H, $H_3CC(6)$), 1.15 (dt, $J_{HP} = 21.2$, $J_{HH} = 7.6$, 3H, CH_2CH_3), 1.12 (d, $J = 6.6$, 3H, $(CH_3)_a(CH_3)_bCHN$), 1.02 (d, $J = 6.8$, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (100 MHz) 75.3 ($J = 9.2$, C(6)), 47.2 ($J = 5.3$, $(CH_3)_2CHN$), 38.0 (C(4)), 34.5 ($J = 5.3$, C(5)), 23.5 ($J = 90.0$, CH_2CH_3), 22.9 ($J = 7.6$, $CH_3C(6)$), 21.2 ($J = 3.1$, $(CH_3)_a(CH_3)_bCHN$), 20.4 ($J = 3.8$, $(CH_3)_a(CH_3)_bCHN$), 7.3 ($J = 4.6$, CH_2CH_3); ^{31}P NMR (161.9 MHz) 92.47; IR (CCl_4) 2973 (s), 1175 (s); MS (70 eV) 222 (M + 1^+, 12), 221 (M^+, 100); TLC R_f 0.20 (benzene); $[\alpha]_D$ −72.16° (CH_2Cl_2, $c = 0.51$). Anal. Calcd for $C_9H_{20}NOPS$ (221.30): C, 48.85; H, 9.11; N, 6.33; P, 14.00; S, 14.49. Found: C, 48.88; H, 9.16; N, 6.32; P, 13.96; S, 14.42.

(*S*)-(2*l*,6*l*)-2-(Methoxymethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide (*cis*-18). By following the general procedure, from Lawesson's reagent (340 mg, 1.01 mmol, 1.05 equiv) and *cis*-**11** (425 mg, 1.92 mmol) in anhydrous toluene (18 mL) after being heated at 80 °C for 4.5 h was obtained the crude thiophosphonamidate as a yellowish oil. The residual oil was purified by SiO_2 column chromatography (petroleum ether/Et_2O, 3/1) to give 358 mg (78.5%) of *cis*-**18** as a white solid. An analytical sample was obtained by recrystallization from pentane: mp 42−43 °C (pentane); ^1H NMR (400 MHz) 4.62−4.55 (m, 1H, HC(6)), 3.89−3.76 (m, 3H, $(CH_3)_2CHN$, $H_2C(1')$), 3.45 (d, 3H, OCH_3), 3.18−3.03 (m, 2H, $H_2C(4)$), 1.90−1.78 (m, 2H, $H_2C(5)$), 1.33 (dd, $J = 6.1$, 1.2, 3H, $H_3CC(6)$), 1.18 (d, $J = 6.8$, 3H, $(CH_3)_a(CH_3)_bCHN$), 1.10 (d, $J = 6.8$, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (100 MHz) 74.1 ($J = 116.0$, C(1')), 71.8 ($J = 7.6$, C(6)), 60.9 ($J = 10.7$, OCH_3), 47.1 ($J = 6.1$, $(CH_3)_2CHN$), 36.9 (C(4)), 33.6 ($J = 3.1$, C(5)), 22.3 ($J = 8.4$, $CH_3C(6)$), 20.7 ($J = 6.9$, $(CH_3)_a(CH_3)_bCHN$), 19.2 ($(CH_3)_a(CH_3)_bCHN$); ^{31}P NMR (161.9 MHz) 84.96; IR (CCl_4) 2974 (s), 1174 (s); MS (70 eV) 237 (M^+, 5), 192 (100); TLC R_f 0.52 (petroleum Et_2O/Et_2O, 3/1); $[\alpha]_D$ +40.53° (CH_2Cl_2, $c = 0.76$). Anal. Calcd for $C_9H_{20}NO_2PS$ (237.30): C, 45.55; H, 8.50; N, 5.90; P, 13.05; S, 13.51. Found: C, 45.55; H, 8.49; N, 5.92; P, 12.99; S, 13.47.

(*S*)-(2*u*,6*l*,1'*u*)-3-(1-Methylethyl)-2-(1'-phenylethyl)-6-methyl-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2*u*,6*l*,1'*l*)-3-(1-Methylethyl)-2-(1'-phenylethyl)-6-methyl-1,3,2-oxazaphosphorinane 2-Oxide ((*u*)-19 and (*l*)-19). In an oven-dried, 50 mL, three-necked, flask equipped with a stir bar, thermometer, septum, and N_2 inlet was placed *cis*-**9** (87 mg, 0.33 mmol) in anhydrous THF (15 mL). The solution was cooled to an internal temperature of −72 °C. To this solution was added *t*-BuLi (1.58 M in pentane; 268 μL, 42.3 mmol, 1.3 equiv), and a pale yellow color appeared. After the mixture was stirred for 30 min, methyl iodide (102 μL, 1.63 mmol, 5 equiv) was added. The color faded in about 10 min. H_2O (4 mL) was added after 20 min. After the reaction mixture had warmed to rt, THF was removed under reduced pressure. H_2O (5 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated to afford a white solid. ^{31}P NMR

spectroscopy showed a ratio of 24/1 (*u*/*l*) and HPLC analysis showed a ratio of 97/3, (*u*/*l*). The crude residue was purified by MPLC (EtOAc/*i*-PrOH, 99/1) to obtain 82 mg (89.5%) of (*u*)-**19** and 3 mg (3.4%) of (*l*)-**19**. An analytical sample of (*u*)-**19** was obtained by recrystallization from pentane. Data for (*u*)-**19**: mp 108−109.5 °C (pentane); ^{1}H NMR (300 MHz) 7.33−7.19 (m, 5H, Ph), 4.42−4.32 (m, 1H, HC(6)), 3.87−3.75 (m, 1H, $(CH_3)_2CHN$), 3.22 (qd, J_{HH} = 7.4, J_{HP} = 0.7, 1H, HC(1′)), 2.95−2.84 (m, 1H, $H_{ax}C(4)$), 2.59−2.48 (m, 1H, $H_{eq}C(4)$), 1.62 (dd, J_{HP} = 17.5, J_{HH} = 7.4, 3H, $H_3C(2')$), 1.61−1.52 (m, 1H, $H_{eq}C(5)$), 1.21 (d, J = 6.6, 3H, $H_3C(9)$), 1.21 (dd, J_{HH} = 4.5, J_{HP} = 1.4, 3H, $H_3C(7)$), 0.84−0.70 (m, 1H, $H_{ax}C(5)$), 1.08 (d, J_{HH} = 6.8, 3H, $H_3C(9)$); ^{13}C NMR (75.5 MHz) 139.6 (J = 7.3, C_{ipso}), 128.7 (J = 5.6, C_{ortho}), 127.8 (J = 2.1, C_{para}), 126.5 (J = 3.2, C_{meta}), 72.3 (J = 8.2, C(6)), 46.3 (J = 4.2, $(CH_3)_2CHN$), 40.6 (J = 129.1, C(1′)), 37.2 C(4), 31.9 (J = 3.5, C(5)), 21.9 (J = 8.2, C(7)), 20.8 (C(9)), 20.2 (J = 6.0, C(9)), 15.4 (J = 4.9, C(2′)); ^{31}P NMR (121.65 MHz) 29.11; IR (CCl_4) 3031 (w), 2975 (s), 1248 (s, P=O); MS (70 eV) 281 (M^+, 3.5), 134 (100); TLC R_f 0.29 (EtOAc/*i*-PrOH, 49/1); HPLC t_R 8.40 min (Supelco LC-Si, EtOAc/*i*-PrOH, 10.1/1, 1.0 mL/min); $[\alpha]_D$ +37.4° (CH_2Cl_2, c = 0.91). Anal. Calcd for $C_{15}H_{24}NO_2P$ (281.32): C, 64.04; H, 8.60; N, 4.98; P, 11.01. Found: C, 64.05; H, 8.61; N, 5.00; P, 10.93. Data for (*l*)-**19**: ^{1}H NMR (300 MHz) 7.31−7.19 (m, 5H, Ph), 4.41−4.30 (m, 1H, HC(6)), 3.87−3.76 (m, 1H, $(CH_3)_2CHN$), 3.19 (dq, J_{HP} = 22.0, J_{HH} = 7.4, 1H, HC(1′)), 3.00−2.88 (m, 1H, $H_{ax}C(4)$), 2.77−2.67 (m, 1H, $H_{eq}C(4)$), 1.64−1.56 (m, 1H, $H_{eq}C(5)$), 1.60 (dd, J_{HP} = 17.8, J_{HH} = 7.4, 3H, $H_3C(2')$), 1.20 (dd, J_{HH} = 6.0, J_{HP} = 1.1, 3H, $H_3C(7)$), 1.16 (d, J = 6.6, 3H, $H_3C(9)$), 0.95 (d, J = 6.8, 3H, $H_3C(9)$), 0.91−0.79 (m, 1H, $H_{ax}C(5)$); ^{31}P NMR (121.65 MHz) 28.19; MS (70 eV) 281 (M^+, 4), 134 (100); High-resolution MS calcd for $C_{15}H_{24}NO_2P$ 281.1545, found 281.1544; TLC R_f 0.38 (EtOAc/*i*-PrOH, 49/1); HPLC t_R 6.39 min (Supelco LC-Si, EtOAc/*i*-PrOH, 10.1/1, 1.0 mL/min).

(*S*)-(2*u*,6*l*,1′*u*)-2-(1′,2′-Diphenylethyl)-3-(1-methylethyl)-6-methyl-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2*u*,6*l*,1′*l*)-2-(1′,2′-Diphenylethyl)-3-(1-methylethyl)-6-methyl-1,3,2-oxazaphosphorinane 2-Oxide ((*u*)-20 and (*l*)-20). In an oven-dried, 25 mL, three-necked, round-bottomed flask equipped with a stir bar, thermometer, septum, and N_2 inlet was placed *cis*-**9** (93 mg, 0.35 mmol) in anhydrous THF (17 mL). The solution was cooled to an internal temperature of −72 °C, *t*-BuLi (1.58 M in pentane; 287 μL, 0.454 mmol, 1.3 equiv) was added, and a pale yellow color appeared. After the mixture was stirred for 30 min, benzyl bromide (125 μL, 1.05 mmol, 3.0 equiv) was added. The color faded in about 20 min. The mixture was stirred at this temperature for 1 h, and H_2O (2 mL) was added. The reaction mixture was warmed to rt, and THF was removed under reduced pressure. H_2O (3 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated to afford a white solid. ^{31}P NMR spectroscopy showed a ratio of 15.6/1 (*u*/*l*) and HPLC analysis showed a ratio of 15.6/1 (*u*/*l*). The crude residue was purified by MPLC (EtOAc/*i*-PrOH, 32.3/1) to obtain 103 mg (83%) of (*u*)-**20** and 7 mg (5.5%) of (*l*)-**20**. An analytical sample of (*u*)-**20** was obtained by recrystallization from hexane. Data for (*u*)-**20:** mp 123.5−124.8 °C (hexane); ^{1}H NMR (300 MHz) 7.28−7.00 (m, 10 H, Ph), 4.48−4.39 (m, 1H, HC(6)), 3.94−3.83 (m, 1H, $(CH_3)_2CHN$), 3.65 (ddd, J_{gem} = 13.6, J_{HP} = 9.3, J_{HH} = 2.31, 1H, $H_aH_bC(2')$), 3.37 (ddd, J_{HP} = 20.1, J_{HH} = 12.2, J_{HH} = 2.4, 1H, HC(1′)), 3.22 (ddd, J_{gem} = 13.6, J_{HH} = 12.2, J_{HP} = 5.5, 1H, $H_aH_bC(2')$), 2.95−2.83 (m, 1H, $H_{ax}C(4)$), 2.52−2.41 (m, 1H, $H_{eq}C(4)$), 1.59−1.54 (m, 1H, $H_{eq}C(5)$), 1.28 (dd, J_{HH} = 6.4, J_{HP} = 1.0, 3H, $H_3C(7)$), 1.23 (d, J = 6.6, 3H, $H_3C(9)$), 1.02 (d, J = 6.8, 3H, $H_3C(9)$), 0.92−0.78 (m, 1H, $H_{ax}C(5)$); ^{13}C NMR (75.5 MHz) 139.9 (J = 17.1, C_{ipso}), 136.8 (J = 7.1, $C_{ipso'}$), 129.6 (J = 6.0, C_{ortho}), 128.7 ($C_{ortho'}$), 127.9 ($C_{para'}$), 127.7 (J = 2.1, C_{para}), 126.6 (J = 3.0, C_{meta}), 125.7 ($C_{meta'}$), 72.6 (J = 8.0, C(6)), 49.3 (J = 127.2, C(1′)), 46.3 (J = 4.5, $(CH_3)_2CHN$), 37.0 (C(4)), 35.5 (J = 2.2, C(2′)), 31.9 (J = 3.4, C(5)), 22.0 (J = 8.2, C(7)), 20.8 (C(9)), 20.1 (J = 6.0, C(9)); ^{31}P NMR (121.65 MHz) 27.94; IR (CCl_4) 3031 (s), 2975 (s), 1244 (s, P=O); MS (70 eV) 357 (M^+, 20), 162 (100); TLC R_f 0.47 (EtOAc/*i*-PrOH, 49/1); HPLC t_R 8.38 min (Supelco LC-Si, EtOAc/*i*-PrOH, 15.6/1 , 1.0 mL/min); $[\alpha]_D$ −46° (CH_2Cl_2, c = 0.6). Anal. Calcd for $C_{21}H_{28}NO_2P$ (357.41): C, 70.57; H, 7.90; N, 3.92; P, 8.67. Found: C, 70.57; H, 7.92; N, 3.91; P, 8.48. Data for (*l*)-**20**: ^{1}H NMR (300 MHz) 7.37−6.98 (m, 10H, Ph), 4.47−4.39 (m, 1H, HC(6)), 3.77−3.67 (m, 1H, $(CH_3)_2CHN$), 3.58 (dd, J_{gem} = 11.6, J_{HP} = 8.8, 1H, $H_aH_bC(2')$), 3.27−3.12 (m, 2H, HC(1′), $H_aH_bC(2')$), 3.05−2.93 (m, 1H, $H_{ax}C(4)$), 2.87−2.77 (m, 1H, $H_{eq}C(4)$), 1.78−1.71 (m, 1H, $H_{eq}C(5)$), 1.24 (dd, J_{HH} = 6.5, J_{HP} = 1.0, 3H, $H_3C(7)$), 1.25−1.08 (m, 1H, $H_{ax}C(5)$), 1.14 (d, J = 6.6, 3H, $H_3C(9)$), 0.75 (d, J = 6.8, 3H, $H_3C(9)$); ^{31}P NMR (121.65 MHz) 25.60; MS (70 eV) 357 (M^+, 23), 134 (100); High-resolution MS calcd for $C_{20}H_{28}NO_2P$ 357.1858, found 357.1863; TLC R_f 0.54 (EtOAc/*i*-PrOH, 49/1); HPLC t_R 6.20 min (Supelco LC-Si, EtOAc/*i*-PrOH, 15.6/1, 1.0 mL/min).

(*S*)-(2*l*,6*l*,1′*u*)-6-Methyl-3-(1-methylethyl)-2-(1′-phenylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*u*)-21). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed *cis*-**16** (155 mg, 0.55 mmol) in anhydrous THF (5.5 mL). The solution was cooled to −78 °C and *t*-BuLi (2.19 M in pentane, 275 μL, 0.60 mmol, 1.1 equiv) was added. The resulting yellowish solution was stirred at this temperature for 10 min. Anhydrous methyl iodide (102 μL, 1.64 mmol, 3.0 equiv) was added with instant color dissipation. The reaction mixture was stirred for 30 min followed by addition of H_2O (7 mL). The resulting slurrish mixture was gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of >9000/1 (*u*/*l*). The residual oil was purified by SiO_2 column chromatography (hexane/EtOAc, 8/1) to yield 160 mg (98.5%) of (*u*)-**21** as a white solid. An analytical sample was obtained by recrystallization from pentane: mp 81.5−84 °C (pentane); ^{1}H NMR (400 MHz) 7.34−7.22 (m, 5H, Ph), 4.58−4.49 (m, 1H, HC(6)), 3.71 (dsept, J_{HP} = 19.8, J_{HH} = 6.6, 1H, $(CH_3)_2CHN$), 3.41 (dq, J_{HP} = 14.9. J_{HH} = 7.6, 1H, HC(1′)), 2.97 (ddt, J_{HH} = 12.4, J_{HP} = J_{HH} = 9.4, J_{HH} = 4.8, 1H, $H_{ax}C(4)$), 2.56 (ddt, J_{HP} = 17.1, J_{HH} = 12.2, 5.0, 1H, $H_{eq}C(4)$), 1.75−1.65 (m, 1H, $H_{eq}C(5)$), 1.69 (dd, J_{HP} = 20.0, J_{HH} = 7.3, 3H, $H_3C(2')$), 1.37−1.27 (m, 1H, $H_{ax}C(4)$), 1.32 (dd, J_{HH} = 6.1, J_{HP} = 1.5, 3H, $H_3C(6)$), 1.17 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.80 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (100 MHz) 139.9 (J = 8.4, C_{ipso}), 128.8 (J = 6.9, C_{ortho}), 127.9 (J = 2.3, C_{meta}), 126.7 (J = 3.1, C_{para}), 70.6 (J = 7.6, C(6)), 47.3 (J = 93.8, C(1′)), 47.2 (J = 5.3, $(CH_3)_2CHN$), 36.6 (C(4)), 33.7 (J = 3.1, C(5)), 22.2 (J = 9.2, $CH_3C(6)$), 20.4 (J = 8.4, $(CH_3)_a(CH_3)_bCHN$), 18.7 ($(CH_3)_a(CH_3)_bCHN$), 16.7 (J = 1.5, C(2′)); ^{31}P NMR (161.9 MHz) 95.07; IR ($CHCl_3$) 3020 (s), 2978 (m), 1217 (s); MS (70 eV) 297 (M^+, 4), 192 (100); TLC R_f 0.47 (hexane/EtOAc, 8/1); $[\alpha]_D$ +56.7 ($CHCl_3$, c = 0.79). Anal. Calcd for $C_{15}H_{24}NOPS$ (297.39): C, 60.58; H, 8.13; N, 4.71; P, 10.41; S, 10.78. Found: C, 60.55; H, 8.14; N, 4.70; P, 10.39; S, 10.72.

(*S*)-(2*l*,6*l*,1′*u*)-2-(1′,2′-Diphenylethyl)-3-(1-methylethyl)-6-methyl-1,3,2-oxazaphosphorinane 2-Sulfide ((*u*)-22). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed *cis*-**16** (100 mg, 0.354 mmol) in anhydrous THF (3.5 mL). The solution was cooled to −78 °C and *t*-BuLi (2.19 M in pentane, 178 μL, 0.39 mmol, 1.1 equiv) was added. The resulting yellowish solution was stirred at this temperature for 10 min. Anhydrous benzyl bromide (126 μL, 1.06 mmol, 3.0 equiv) was added with instant color dissipation. The reaction mixture was stirred for 1 h followed by addition of H_2O (6 mL). The resulting slurrish mixture was gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of >6500/1 (*u*/*l*). The residual oil was purified by SiO_2 column chromatography (benzene) to yield 123 mg (93%) of (*u*)-**22** as a white solid. An analytical sample was obtained by recrystallization from hexane: mp 113−113.5 °C (hexane); ^{1}H NMR (400 MHz) 7.26−6.95 (m, 10H, Ar), 4.64−4.58 (m, 1H, HC(6)), 3.88 (ddd, J_{HH} = 13.7, J_{HP} = 11.0, J_{HH} = 2.7, 1H, $H_aH_bC(2')$), 3.64 (dsept, J_{HP} = 20.0, J_{HH} = 6.8, 1H, $(CH_3)_2CHN$), 3.48 (ddd, J_{HP} = 14.2, J_{HH} = 12.0, J_{HH} = 2.7, 1H, HC(1′)), 3.11 (ddd, J_{HH} = 13.7, J_{HH} = 12.0, J_{HP} = 4.6, $H_aH_bC(2')$), 3.03−2.94 (m, 1H, $H_{ax}C(4)$), 2.55 (ddt, J_{HP} = 17.3, J_{HH} = 12.2, 4.9, 1H, $H_{eq}C(4)$), 1.77−1.71 (m, 1H, $H_{eq}C(5)$), 1.47−1.37 (m, 1H, $H_{ax}C(5)$), 1.38 (dd, J_{HH} = 6.2, J_{HP} = 1.1, 3H, $H_3C(6)$), 1.18 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.65 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (100 MHz) 139.6 (J = 18.3, C_{ipso}), 136.3 (J = 7.6, $C_{ipso'}$), 129.5 (J = 6.9, C_{ortho}), 128.6 ($C_{ortho'}$), 127.80 ($C_{meta'}$), 127.7 (J = 1.5, C_{meta}), 126.7 (J = 3.1, C_{para}), 125.7

($C_{para'}$), 70.9 (J = 7.6, C(6)), 55.7 (J = 91.6, C(1')), 47.0 (J = 4.6, $(CH_3)_2CHN$), 36.8 (C(4)), 36.5 (C(2')), 33.7 (J = 2.3, C(5)), 22.2 (J = 9.2, $CH_3C(6)$), 20.9 (J = 9.2, $(CH_3)_a(CH_3)_bCHN$), 18.4 ($(CH_3)_a(CH_3)_bCHN$); ^{31}P NMR (161.9 MHz) 94.25; IR (CCl_4) 3065 (w), 2971 (s), 1171 (s); MS (70 eV) 373 (M^+, 2), 160 (100); TLC R_f 0.5 (benzene); $[\alpha]_D$ −23.5° ($CHCl_3$, c = 0.79). Anal. Calcd for $C_{21}H_{28}NOPS$ (373.50): C, 67.53; H, 7.56; N, 3.75; P, 8.29; S, 8.58. Found: C, 67.60; H, 7.57; N, 3.75; P, 8.25; S, 8.48.

(*S*)-(2*u*,6*l*,1'*l*)-6-Methyl-3-(1-methylethyl)-2-(1'-methylpentyl)-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2*u*,6*l*,1'*u*)-6-Methyl-3-(1-methylethyl)-2-(1'-methylpentyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*l*)-23 and (*u*)-23). In an oven-dried, 100 mL, three-necked, round-bottomed flask equipped with a thermometer, stir bar, gas inlet, and septum was placed *cis*-**10** (289 mg, 1.41 mmol) in anhydrous THF (45 mL). The solution was cooled to an internal temperature of −73 °C under nitrogen. To this solution was added *t*-BuLi (1.80 M in pentane, 780 μL, 1.41 mmol, 1.0 equiv) with the appearance of a bright yellow color. The resulting reaction mixture was stirred at this temperature for 30 min. *n*-Butyl iodide (800 μL, 7.03 mmol, 5.0 equiv) was added over 10 s and the mixture was stirred for an additional 1.5 h. H_2O (10 mL) was added, and the mixture was allowed to warm to rt. The aqueous layer was separated and extracted with TBME (4 × 50 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated under reduced pressure to give a pale-yellow oil. ^{31}P NMR spectroscopic analysis showed a diastereomeric ratio of 19/1 (*l*/*u*). The residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 19/1) to yield **23** (345 mg, 94%) as a colorless viscous oil. An analytical sample of (*l*)-**23** was obtained by Kugelrohr distillation. Data for (*l*)-**23**: bp 100 °C (0.1 Torr, air bath); ^1H NMR (300 MHz) 4.51−4.41 (m, 1H, HC(6)), 3.78−3.66 (m, 1H, $(CH_3)_2CHN$), 3.09 (ddd, J = 22.3, 11.1, 5.6, 1H, $H_{ax}C(4)$), 3.03−2.92 (m, 1H, $H_{eq}C(4)$), 1.89−1.73 (m, 3H, $H_{eq}C(5)$, HC(1'), $H_aH_bC(2')$), 1.71−1.57 (m, 1H, $H_{ax}C(5)$), 1.49−1.35 (m, 1H, $H_aH_bC(2')$), 1.34−1.15 (m, 4H, $H_2C(3')$, $H_2C(4')$), 1.28 (d, J = 6.4, 3H, $H_3CHC(6)$), 1.21 (d, J = 6.6, 3H, $(H_3C)_2CHN$), 1.10 (d, J = 6.6, 3H, $(H_3C)_2CHN$), 1.07 (dd, J = 17.1, 7.0, 3H, $H_3CCH(1')$), 0.87 (t, J = 6.9, 3H, $H_3C(5')$); ^{13}C NMR (75.5 MHz) 71.2 (J = 7.7, C(6)), 46.0 (J = 4.2, $(CH_3)_2CHN$), 36.9 (C(4)), 33.1 (J = 2.8, C(5)), 31.9 (J = 133.6, C(1')), 29.8 (J = 14.1, C(3')), 19.5 (J = 3.4, C(2')), 22.4 (C(4')), 22.1 (J= 8.2, C(7)), 20.4 ($C(9_a)$), 20.2 (J = 6.5, $C(9_b)$), 13.8 (C(5')), 13.7 (J = 4.6, C(6')); ^{31}P NMR (121.65 MHz) 34.94; IR (CCl_4) 2967 (s), 1219 (s), 1177 (s); MS (70 eV) 261 (M^+, 11), 246 (100); TLC R_f 0.33 (EtOAc/*i*-PrOH, 19/1); $[\alpha]_D$ +11.14° (CH_2Cl_2, c = 1.76). Anal. Calcd for $C_{13}H_{28}NO_2P$ (261.33): C, 59.74; H, 10.80; N, 5.36; P, 11.85. Found: C, 59.65; H, 10.70; N, 5.33; P, 11.72. Data for (*u*)-**23**: ^1H NMR (300 MHz) 4.50−4.40 (m, 1H, HC(6)), 3.79−3.67 (m, 1H, $(CH_3)_2CHN$), 3.09 (ddd, J = 22.6, 11.4, 6.0, 1H, $H_{ax}C(4)$), 3.04−2.92 (m, 1H, $H_{eq}C(4)$), 1.90−1.85 (m, 1H, $H_{eq}C(5)$), 1.82−1.57 (m, 3H, HC(1'), $H_aH_bC(2')$, $H_{ax}C(5)$), 1.46−1.36 (m, 1H, $H_aH_bC(2')$), 1.33−1.16 (m, 4H, $H_2C(3')$, $H_2C(4')$), 1.27 (d, J = 6.2, 3H, $H_3CC(6)$), 1.20 (d, J = 6.6, 3H, $(H_3C)_a(H_3C)_bCHN$), 1.13 (dd, J = 20.2, 7.2, 3H, $H_3CC(1'')$), 1.10 (d, J = 6.7, 3H, $(H_3C)_a(H_3C)_bCHN$), 0.88 (t, J = 7.0, 3H, $H_3C(5')$); ^{31}P NMR (121.65 MHz) 35.01; MS (70 eV) 261 (M^+, 8), 246 (100); High-resolution MS calcd for $C_{13}H_{28}NO_2P$ 261.1858, found 281.1859; TLC R_f 0.31 (EtOAc/*i*-PrOH, 19/1).

(*S*)-(2*u*,6*l*,1'*l*)-2-(1',3'-Dimethylbutyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2*u*,6*l*,1'*u*)-2-(1',3'-Dimethylbutyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*l*)-24 and (*u*)-24). In an oven-dried, 100 mL, three-necked, round-bottomed flask equipped with a thermometer, stir bar, gas inlet, and septum was placed *cis*-**10** (320 mg, 1.56 mmol) in anhydrous THF (50 mL). The solution was cooled to an internal temperature of −73 °C under nitrogen. To this solution was added *t*-BuLi (1.80 M in pentane, 865 μL, 1.56 mmol, 1.0 equiv) with the appearance of a bright-yellow color. The resulting reaction mixture was stirred at this temperature for 30 min. 1-Iodo-2-methylpropane (898 μL, 7.8 mmol, 5.0 equiv) was added over 10 s, and the mixture was stirred for an additional 3 h. H_2O (10 mL) was added, and the mixture was allowed to warm to rt. The aqueous layer was separated and extracted with TBME (4 × 50 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated under reduced pressure to give a pale-yellow oil. ^{31}P NMR spectroscopic analysis showed a diastereomeric ratio of 49/1 (*l*/*u*). The residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 19/1) to yield **24** (355 mg, 87%) as a colorless liquid. An analytical sample of (*l*)-**24** was obtained by Kugelrohr distillation. Data for (*l*)-**24**: bp 95 °C (0.07 Torr, air bath); ^1H NMR (300 MHz) 4.54−4.44 (m, 1H, HC(6)), 3.82−3.70 (m, 1H, $(CH_3)_2CHN$), 3.12 (ddd, J = 22.5, 11.3, 5.9, 1H, $H_{ax}C(4)$), 3.06−2.95 (m, 1H, $H_{eq}C(4)$), 1.98−1.82 (m, 2H, $H_{eq}C(5)$, $H_aH_bC(2')$), 1.76−1.63 (m, 2H, HC(1'), HC(3')), 1.62−1.51 (m, 1H, $H_{ax}C(5)$), 1.39−1.27 (m, 1H, $H_aH_bC(2')$), 1.31 (dd, J = 6.5, 1.0, 3H, $H_3C(7)$), 1.24 (d, J = 6.6, 3H, $H_3C(9_a)$), 1.14 (d, J = 6.8, 3H, $H_3C(9_b)$), 1.08 (dd, J = 18.7, 7.1, 3H, $H_3CHC(1')$), 0.94 (d, J = 6.4, 3H, $H_3C(4')$), 0.86 (d, J = 6.4, 3H, $H_3C(5')$); ^{13}C NMR (75.5 MHz) 71.1 (J = 7.5, C(6)), 45.9 (J = 4.8, $(CH_3)_2CHN$), 38.4 (J = 3.6, C(4)), 36.7 (C(5')), 33.0 (J = 3.2, C(2')), 29.6 (J = 134.07, C(1')), 24.9 (J = 14.8, C(3')), 23.5 (C(4')), 22.0 (J = 8.4, C(7)), 20.4 ($C(9_a)$), 20.3 (C(5')), 20.2 (J = 6.8, $C(9_b)$), 13.5 (J = 4.8, $H_3CC(1')$); ^{31}P NMR (121.65 MHz) 35.37; IR (CCl_4) 2961 (s), 1260 (s), 1231 (s); MS (70 eV) 261 (M^+, 5), 246 (100); TLC R_f 0.28 (EtOAc/*i*-PrOH, 19/1); $[\alpha]_D$ +3.51° (CH_2Cl_2, c = 0.855). Anal. Calcd for $C_{13}H_{28}NO_2P$ (261.33): C, 59.74; H, 10.80; N, 5.36; P, 11.85. Found: C, 59.70; H, 10.72; N, 5.43; P, 11.80. Data for (*u*)-**24**: ^1H NMR (300 MHz) 4.51−4.42 (m, 1H, HC(6)), 3.79−3.72 (m, 1H, $(H_3C)_2CHN$), 3.10 (ddd, J = 22.4, 11.3, 6.3, 1H, $H_{ax}C(4)$), 3.07−2.93 (m, 1H, $H_{eq}C(4)$), 1.96−1.81 (m, 2H, $H_{eq}C(5)$, $H_aH_bC(2')$), 1.75−1.59 (m, 2H, HC(1'), HC(3')), 1.51−1.39 (m, 1H, $H_{ax}C(5)$), 1.28 (dd, J = 6.0 , 1.0, 3H, $H_3CC(6)$), 1.23−1.09 (m, 1H, $H_aH_bC(2')$), 1.22 (d, J = 6.6, 3H, $(H_3C)_a(H_3C)_bCHN$), 1.13 (dd, J = 18.4, 7.1, 3H, $H_3CC(1')$), 1.11 (d, J = 6.7, 3H, $(H_3C)_a(H_3C)_bCHN$), 0.92 (d, J = 6.5, 3H, $H_3C(4')$), 0.82 (d, J = 6.5, 3H, $H_3C(5')$); ^{31}P NMR (121.65 MHz) 35.58; MS (70 eV) 261 (M^+, 6), 146 (100); High-resolution MS calcd for $C_{13}H_{28}NO_2P$ 261.1858, found 261.1859; TLC R_f 0.26 (EtOAc/*i*-PrOH, 19/1).

(*S*)-(2*u*,6*l*,1'*l*)-6-Methyl-3-(1-methylethyl)-2-(1'-methyl-2'-phenylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*l*)-25). In an oven-dried, 100 mL, three-necked, round-bottomed flask equipped with a thermometer, stir bar, gas inlet, and septum was placed *cis*-**10** (311 mg, 1.51 mmol) in anhydrous THF (50 mL). The solution was cooled to an internal temperature of −73 °C under nitrogen. To this solution was added *t*-BuLi (1.53 M in pentane, 989 μL, 1.51 mmol, 1.0 equiv) with the appearance of a bright yellow color. The resulting reaction mixture was stirred at this temperature for 30 min. Benzyl bromide (540 μL, 4.54 mmol, 3.0 equiv) was added over 10 s, and the mixture was stirred for an additional 1.5 h. H_2O (7 mL) was added, and the mixture was allowed to warm to rt. The aqueous layer was separated and extracted with TBME (4 × 50 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated under reduced pressure to give a pale-yellow oil. ^{31}P NMR spectroscopic analysis showed a diastereomeric ratio of 19/1 (*l*/*u*). The residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 19/1) to yield **25** (429 mg, 96%) as a colorless viscous oil. An analytical sample of (*l*)-**25** was obtained by recrystallization from pentane. Data for (*l*)-**25**: mp 73−74 °C (pentane); ^1H NMR (300 MHz) 7.28−7.11 (m, 5H, Ph), 4.55−4.46 (m, 1H, HC(6)), 3.84−3.72 (m, 1H, $(CH_3)_2CHN$), 3.31 (ddd, J = 12.6, 8.9, 2.7, 1H, $H_aH_bC(2')$), 3.12 (ddd, J = 22.3, 11.1, 5.7, 1H, $H_{ax}C(4)$), 3.08−2.95 (m, 1H, $H_{eq}C(4)$), 2.42 (dt, J = 12.4, 5.7, 1H, $H_aH_bC(2')$), 2.17−2.00 (m, 1H, HC(1')), 1.92−1.87 (m, $H_{eq}C(5)$), 1.74−1.60 (m, 1H, $H_{ax}C(5)$), 1.31 (d, J = 6.1, 3H, $H_3C(6)$), 1.24 (d, J = 6.6, 3H, $(H_3C)_a(H_3C)_bCHN$), 1.10 (d, J = 6.8, 3H, $(H_3C)_a(H_3C)_bCHN$), 0.95 (dd, J_{HP} = 18.3, J_{HH} = 7.0, 3H, $H_3CC(1')$); ^{13}C NMR (75.5 MHz) 139.8 (J = 17.55, C_{ipso}), 128.6 (C_{ortho}), 127.9 (C_{para}), 125.7 (C_{meta}), 71.4 (J = 7.8, C(6)), 45.9 (J = 4.4, $(H_3C)_2CHN$), 36.7 (C(4)), 35.9 (J = 1.9, C(2')), 34.1 (J = 133.7, C(1')), 32.8 (J = 3.1, C(5)), 21.9 (J = 8.2, $H_3CC(6)$), 20.2 ($(H_3C)_2CHN$), 20.1 (J = 6.2, $(H_3C)_2CHN$), 13.0 (J = 4.3, $H_3CC(1')$); ^{31}P NMR (121.65 MHz) 33.31; IR (CCl_4) 3027 (w), 2971 (s), 1248 (s), 1217 (s); MS (70 eV) 295 (M^+, 22), 162 (100); TLC R_f 0.25 (EtOAc/*i*-PrOH, 19/1); HPLC t_R 12.70 min (Supelco LC-Si, EtOAc/*i*-PrOH, 15.6/1, 1.0 mL/min); $[\alpha]_D$ −46.9° (CH_2Cl_2, c = 1.3). Anal. Calcd for $C_{16}H_{26}NO_2P$ (295.35): C, 65.06; H, 8.87; N, 4.74; P, 10.49. Found: C, 64.89; H, 8.87; N, 4.78; P, 10.51.

(*S*)-(2*l*,6*l*,1'*l*)-6-Methyl-3-(1-methylethyl)-2-(1'-methylpentyl)-1,3,2-oxazaphosphorinane 2-Sulfide and (*S*)-(2*l*,6*l*,1'*u*)-6-Methyl-3-(1-methylethyl)-2-(1'-methylpentyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*l*)-26 and (*u*)-26). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed *cis*-**17**

(124 mg, 0.56 mmol) in anhydrous THF (5.6 mL). The solution was cooled to −78 °C and *n*-BuLi (2.76 M in hexane, 223 μL, 0.62 mmol, 1.1 equiv) was added. The resulting yellowish solution was stirred at this temperature for 30 min. Anhydrous *n*-butyl iodide (319 μL, 2.8 mmol, 5 equiv) was added over 1 min. The reaction mixture was stirred for 5 h followed by addition of H_2O (10 mL). The resulting slurry was gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 15.6/1 (*l*/*u*). The residual oil was purified by SiO_2 column chromatography (hexane/EtOAc, 8/1) to yield 154 mg (99.4%) of **26** as a colorless oil. An analytical sample of **26** was obtained by Kugelrohr distillation. Data for (*l*)-**26** and (*u*)-**26**: bp 85 °C (0.1 Torr, air bath); ^1H NMR (400 MHz) 74.60−4.51 (m, 1H, HC(6)), 3.61 (dsept, J_{HP} = 19.8, J_{HH} = 6.6, 1H, $(CH_3)_2CHN$), 3.14 (dddd, J_{HP} = 18.3, J_{HH} = 10.3, 8.1, 4.2, 1H, $H_{ax}C(4)$), 2.96 (ddt, J_{HP} = 19.3, J_{HH} = 12.2, 4.9, 1H, $H_{eq}C(4)$), 2.09−1.91 (m, 2H, HC(1′), $H_aHbC(2')$), 1.87−1.80 (m, 1H, $H_{eq}C(5)$), 1.67 (dtd, J = 15.6, 10.5, 4.9, 1H, $H_{ax}C(5)$), 1.51−1.41 (m, 1H, $H_aH_bC(2')$), 1.39−1.20 (m, 4H, $H_2C(3')$, $H_2C(4')$), 1.29 (dd, J_{HH} = 6.2, J_{HP} = 1.4, 3H, $CH_3C(6)$), 1.21 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 1.09 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.90 (t, J = 7.1, 3H, $H_3C(5')$); ^{13}C NMR (100 MHz) (*l*)-**26**: 70.0 (J = 6.9, C(6)), 47.1 (J = 4.6, $(CH_3)_2CHN$), 37.8 (J = 97.7, C(1′)), 36.7 (C(4)), 34.2 (J = 2.3, C(5)), 29.8 (J = 15.3, C(3′)), 29.2 (C(2′)), 22.4 (C(4′)), 22.1 (J = 9.2, $CH_3C(6)$), 20.8 (J = 9.2, $(CH_3)_a(CH_3)_bCHN$), 18.2 ($(CH_3)_a(CH_3)_bCHN$), 13.9 (C(5′)), 13.2 (J = 4.6, $C(1')CH_3$), (*u*)-**26**: 70.0 (J = 6.9, C(6)), 47.1 (J = 4.6, $(CH_3)_2CHN$), 38.2 (J = 97.7, C(1′)), 36.7 (C(4)), 34.2 (J = 2.3, C(5)), 29.7 (J = 15.3, C(3′)), 29.2 (C(2′)), 22.4 (C(4′)), 22.1 (J = 9.2, $CH_3C(6)$), 20.8 (J = 9.2, $(CH_3)_a(CH_3)_bCHN$), 18.5 ($(CH_3)_a(CH_3)_bCHN$), 13.9 (C(5′)), 12.9 (J = 2.3, $C(1')CH_3$); ^{31}P NMR (161.9 MHz) (*l*)-**26**: 100.95, (*u*)-**26**: 101.34; IR (neat) 2967 (s), 1179 (s), 1170 (s); MS (70 eV) 277 (M^+, 15), 160 (100); TLC R_f 0.49 (hexane/EtOAc, 8/1); $[\alpha]_D$ +30.0° ($CHCl_3$, c = 0.86). Anal. Calcd for $C_{13}H_{28}NOPS$ (277.41): C, 56.29; H, 10.17; N, 5.05; P, 11.17; S, 11.56. Found: C, 56.30; H, 10.19; N, 5.03; P, 11.14; S, 11.52.

(*S*)-(2*u*,6*l*,1′*u*)-2-(1′-Methoxyethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2*u*,6*l*,1′*l*)-2-(1′-Methoxyethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*u*)-27 and (*l*)-27). In a flame-dried, 50-mL, three-necked, round-bottomed flask fitted with a glass stopper, N_2 inlet, and septum was placed *cis*-**11** (135 mg, 0.61 mmol) in anhydrous THF (20 mL). The solution was cooled to −78 °C, and *t*-BuLi (1.78 M in pentane, 343 μL, 0.61 mmol, 1.0 equiv) was added. The resulting yellowish solution was stirred at this temperature for 30 min. Anhydrous methyl iodide (190 μL, 3.04 mmol, 5.0 equiv) was added with instant color dissipation. The reaction mixture was stirred for 30 min followed by addition of H_2O (3 mL). The resulting slurry was gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 30 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 69/31 (*u*/*l*). The residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOPH, 49/1) to yield 132 mg (92%) of **27** as a colorless oil. An analytical sample of **27** was obtained by Kugelrohr distillation. Data for (*u*)-**27** and (*l*)-**27**: bp 90 °C (0.3 Torr, air bath); ^1H NMR (300 MHz) 4.54−4.45 (m, 1H, HC(6)), 4.01−3.88 (m, 1H, $(CH_3)_2CHN$), 3.53 (qd, J = 6.8, 1.0, 1H, $HC(1')_{major}$), 3.45 (d, J = 0.5, 3H, CH_3O_{minor}), 3.43 (s, 3H, CH_3O_{major}), 3.14−3.05 (m, 2H, $H_2C(4)$), 1.92−1.84 (m, 2H, $H_2C(5)$), 1.39 (dd, J = 16.4, 6.9, 3H, $H_3C(2')_{major}$), 1.40 (dd, J = 16.8, 7.1, 3H, $H_2C(2')_{minor}$), 1.33 (dd, J = 6.1, 1.5, 3H, $H_3CC(6)_{major}$), 1.34 (dd, J = 5.8, 1.7, 3H, $H_3CC(6)_{minor}$), 1.24 (d, J = 6.7, 3H, $(CH_3)_a(CH_3)_bCHN_{major}$), 1.23 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN_{minor}$), 1.17 (d, J = 6.7, 3H, $(CH_3)_a(CH_3)_bCHN_{minor}$), 1.15 (d, J = 6.7, 3H, $(CH_3)_a(CH_3)_bCHN_{major}$); ^{13}C NMR (100 MHz) for (*u*)-**27**: 73.8 (J = 158.7, C(1′)), 73.1 (J = 8.4, C(6)), 58.1 (J = 11.4, OCH_3), 45.9 (J = 4.6, $(CH_3)_2CHN$), 37.3 (C(4)), 32.3 (J = 3.8, C(5)), 22.0 (J = 7.6, $CH_3C(6)$), 20.7 ($(CH_3)_a(CH_3)_bCHN$), 20.1 (J = 3.8, $(CH_3)_a(CH_3)_bCHN$), 14.4 (C(2′)); ^{13}C NMR (100 MHz) for (*l*)-**27**: 74.6 (J = 160.2, C(1′)), 73.0 (J = 8.4, C(6)), 58.4 (J = 9.2, OCH_3), 46.2 (J = 3.8, $(CH_3)_2CHN$), 36.8 (C(4)), 32.3 (J = 3.1, C(5)), 22.0 (J = 8.4, $CH_3C(6)$), 21.0 ($(CH_3)_a(CH_3)_bCHN$), 20.2 (J = 4.6, $(CH_3)_a(CH_3)_bCHN$), 14.5 (J = 2.3, C(2′)); ^{31}P NMR (161.9 MHz) for (*u*)-**27**: 23.05; ^{31}P NMR for (*l*)-**27**: 24.36; IR (neat) 2974 (s), 1225 (s, P=O); MS (70 eV) 235 (M^+, 3), 162 (100); TLC R_f 0.3 (EtOAc/*i*-PrOH, 49/1); $[\alpha]_D$ +14.47° (CH_2Cl_2, c = 0.47). Anal. Calcd for $C_{10}H_{22}NO_3P$ (235.26): C, 51.05; H, 9.43; N, 5.95; P, 13.17. Found: C, 50.89; H, 9.43; N, 5.89; P, 13.06.

(*S*)-(2,6*l*,1′*u*)-2-(1′-Methoxy-2′-phenylethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2,6*l*,1′*l*)-2-(1′-Methoxy-2′-phenylethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*u*)-28 and (*l*)-28). In a flame-dried, 50-mL, three-necked, round-bottomed flask fitted with a glass stopper, N_2 inlet, and septum was placed *cis*-**11** (117 mg, 0.53 mmol) in anhydrous THF (25 mL). The solution was cooled to −78 °C, and *t*-BuLi (1.78 M in pentane, 299 μL, 0.53 mmol, 1.0 equiv) was added. The resulting yellowish solution was stirred at this temperature for 30 min. Anhydrous benzyl bromide (189 μL, 1.59 mmol, 3.0 equiv) was added with instant color dissipation. The reaction mixture was stirred for 30 min followed by addition of H_2O (3 mL). The resulting slurry was gradually warmed to rt. The aqueous layer was separated and extracted with TBME (4 × 30 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 3/1 (*u*/*l*). The residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 49/1) to yield 164 mg (99%) of **28** as a colorless oil. An analytical sample of **28** was obtained by Kugelrohr distillation. Data for (*u*)-**28** and (*l*)-**28**: bp 160 °C (0.4 Torr, air bath); ^1H NMR (400 MHz) 7.31−7.19 (m, 5H, Ph), 4.53−4.48 (m, 1H, HC(6)), 4.06−3.97 (m, 1H, $(CH_3)_2CHN$), 2.84 (ddd, J = 14.2, 10.7, 7.6, 1H, $H_aH_bC(2')_{major}$), 2.78 (ddd, J = 13.9, 11.5, 7.6, 1H, $H_aH_bC(2')_{minor}$), 3.58 (ddd, J = 11.2, 8.3, 2.2, 1H, $H_aH_bC(2')_{minor}$), 3.54 (ddd, J = 11.0, 6.3, 2.7, 1H, $H_aH_bC(2')_{major}$), 3.24−3.06 (m, 3H, HC(1′), $H_2C(4)$), 3.18 (d, J_{HP}= 1.0, 3H, H_3CO_{minor}), 3.18 (s, 3H, H_3CO_{major}), 1.98−1.83 (m, 2H, $H_2C(5)$), 1.34 (d, J = 6.3, 3H, $H_3CC(6)$), 1.27 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN_{major}$), 1.27 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN_{minor}$), 1.23 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_bCHN_{minor}$), 1.18 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_bCHN_{major}$); ^{13}C NMR (100 MHz) for (*u*)-**28**: 138.9 (J = 15.3, C_{ipso}), 129.1 (C_{meta}), 128.0 (C_{ortho}), 126.0 (C_{para}), 80.1(J = 156.4, C(1′)), 73.2 (J = 8.4, C(6)), 60.5 (J = 5.3, OCH_3), 46.2 (J = 4.6, $(CH_3)_2CHN$), 37.4 (C(4)), 37.1 (J = 3.1, C(2′)), 32.3 (J = 3.8, C(5)), 21.9 (J = 6.9, $CH_3C(6)$), 20.9 ($(CH_3)_a(CH_3)_bCHN$), 20.3 (J = 4.6, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR for (*l*)-**28**: 138.8 (J = 16.8, C_{ipso}), 128.9 (C_{meta}), 128.1 (C_{ortho}), 126.1 (C_{para}), 80.8 (J = 156.4, C(1′)), 73.0 (J = 8.4, C(6)), 60.7 (J = 4.6, OCH_3), 46.2 (J = 4.6, $(CH_3)_2CHN$), 36.9 (C(4)), 36.8 (J = 6.1, C(2′)), 32.2 (J = 3.8, C(5)), 22.1 (J = 7.6, $CH_3C(6)$), 21.0 ($(CH_3)_a(CH_3)_bCHN$), 20.4 (J = 4.6, $(CH_3)_a(CH_3)_bCHN$); ^{31}P NMR (161.9 MHz) for (*u*)-**28**: 21.72; ^{31}P NMR for (*l*)-**28**: 23.74; IR (CCl_4) 3030 (w), 2975 (s), 1250 (s); MS (70 eV) 311 (M^+), 162 (100); TLC R_f 0.38 (EtOAc/*i*-PrOH, 49/1). Anal. Calcd for $C_{16}H_{26}NO_3P$ (311.35): C, 61.72; H, 8.42; N,4.50; P, 9.95. Found: C, 61.44; H, 8.42; N, 4.51; P, 9.76.

(*S*)-(2*u*,6*l*,1′*u*)-2-(1′-Methoxyethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*u*)-29). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed *cis*-**18** (45 mg, 0.19 mmol) in anhydrous THF (2 mL). The solution was cooled to −95 °C, and *t*-BuLi (1.9 M in pentane, 110 μL, 0.21 mmol, 1.1 equiv) was added. The resulting yellowish solution was stirred at this temperature for 10 min followed by addition of anhydrous HMPA (146 μL, 0.84 mmol, 4.4 equiv). The reaction mixture was gradually warmed to −78 °C for 20 min. To this solution was added anhydrous methyl iodide (36 μL, 0.57 mmol, 3.0 equiv). The reaction was quenched with H_2O (5 mL) after the reaction mixture was stirred at −78 °C for 4 h and gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 15.6/1 (*u*/*l*). The residual oil was purified by SiO_2 column chromatography (hexane/Et_2O, 3/1) to give 40 mg (84.4%) of **29** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation: bp 65 °C (10^{-6} Torr, air bath); ^1H NMR (400 MHz) 4.60−4.51 (m, 1H, HC(6)), 3.98 (dsept, J_{HP} = 19.8, J_{HH} = 6.6, 1H, $(CH_3)_2CHN$), 3.64 (qd, J_{HH} = 6.8, J_{HP} = 2.2, 1H HC(1′)), 3.47 (d, J = 0.5, 3H, OCH_3), 3.16−3.06 (m, 2H, $H_2C(4)$), 1.91−1.77 (m, 2H $H_2C(5)$), 1.45 (dd, J_{HP} = 18.1, J_{HH} = 6.8, 3H, $H_3C(2')$), 1.33 (dd, J_{HH}

= 6.2, J_{HP} = 1.2, 3H, $H_3CC(6)$), 1.19 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_b$-CHN), 1.10 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_b$CHN); ^{13}C NMR (100 MHz) 80.7 (J = 119.0, C(1')), 71.2 (J = 7.6, C(6)), 58.9 (J = 9.2, C(1')-OCH_3), 47.2 (J = 5.3, $(CH_3)_2CHN$), 37.0 (C(4)), 33.7 (J = 3.1, C(5)), 22.3 (J = 7.6, $CH_3C(6)$), 20.7 (J = 6.1, $(CH_3)_a(CH_3)_b$CHN), 19.5 ($(CH_3)_a(CH_3)_b$CHN), 14.4 (J = 2.3, C(2')); ^{31}P NMR (161.9 MHz) 88.33; IR ($CHCl_3$) 2978 (s), 1223 (w); MS (70 eV) 251 (M^+, 9), 160 (100); TLC R_f 0.33 (hexane/Et_2O, 3/1); $[\alpha]_D$ +44.7° ($CHCl_3$, c = 0.64). Anal. Calcd for $C_{10}H_{22}NOPS$ (251.33): C, 47.79; H, 8.82; N, 5.57; P, 12.32; S, 12.76. Found: C, 47.90; H, 8.89; N, 5.53; P, 12.20; S, 12.59.

(*S*)-(2*l*,6*l*,1'*l*)-2-(1'-Methoxyethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*l*)-29). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed *cis*-**18** (87 mg, 0.37 mmol) in anhydrous ether (3.7 mL). The solution was cooled to −95 °C, and *t*-BuLi (1.9 M in pentane, 213 μL, 0.41 mmol, 1.1 equiv) was added. The resulting yellowish solution was stirred at this temperature for 10 min followed by addition of anhydrous PMDTA (88 μL, 0.423 mmol, 1.15 equiv). The reaction mixture was gradually warmed to −78 °C for 20 min. To this solution was added anhydrous methyl iodide (69 μL, 1.10 mmol, 3.0 equiv). The reaction was quenched with H_2O (5 mL) after the reaction mixture was stirred at −78 °C for 4 h and gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 1/11.1 (*u*/*l*). The residual oil was purified by SiO_2 column chromatography (hexane/Et_2O, 3/1) to give 86 mg (93%) of **29** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation: bp 60 °C (10^{-6} Torr, air bath); ^{1}H NMR (400 MHz) 4.54−4.45 (m, 1H, HC(6)), 4.10−3.92 (m, 1H $(CH_3)_2CHN$), 3.61 (qdd, J_{HH} = 6.8, J_{HP} = 4.1, J_{HH} = 1.0, 1H, HC(1')), 3.45 (dd, J_{HH} = 1.2, J_{HP} = 0.7, 3H, OCH_3), 3.13−3.05 (m, 2H, $H_2C(4)$), 1.94−1.86 (m, 1H, $H_{eq}C(5)$), 1.84−1.71 (m, 1H, $H_{ax}C(5)$), 1.40 (ddd, J_{HP} = 19.0, J_{HH} = 6.8, 1.2, 3H, $H_3C(2')$), 1.31 (dt, J_{HH} = 6.1, J_{HP} = 1.1, J_{HH} = 1.1, 3H, $H_3C(6)$), 1.15 (dd, J_{HH} = 6.6, J_{HP} = 0.8, 3H, $(CH_3)_a(CH_3)_b$CHN), 1.09 (d, J = 6.3, 3H, $(CH_3)_a(CH_3)_b$CHN); ^{13}C NMR (100 MHz) 80.4 (J = 120.5, C(1')), 70.8 (J = 7.6, C(6)), 59.0 (J = 8.4, C(1')OCH_3), 47.6 (J = 5.3, $(CH_3)_2CHN$), 36.7 (C(4)), 33.7 (J = 3.1, C(5)), 22.3 (J = 8.4, $CH_3C(6)$), 20.7 (J = 6.9, $(CH_3)_a(CH_3)_b$CHN), 20.0 ($(CH_3)_a(CH_3)_b$-CHN), 14.8 (J = 5.3, C(2')); ^{31}P NMR (161.9 MHz) 90.18; IR ($CHCl_3$) 3016 (w), 2977 (s), 1231 (w); MS (70 eV) 251 (M^+, 8), 160 (100); TLC R_f 0.33 (hexane/Et_2O, 3/1); $[\alpha]_D$ +63.7° ($CHCl_3$, c = 0.57). Anal. Calcd for $C_{10}H_{22}NOPS$ (251.33): C, 47.79; H, 8.82; N, 5.57; P, 12.32; S, 12.76. Found: C, 47.81; H, 8.83; N, 5.58; P, 12.29; S, 12.72.

(*S*)-(2*l*,6*l*,1'*l*)-6-Methyl-3-(1-methylethyl)-2-(1'-phenylethyl)-1,3,2-oxazaphosphorinane 2-Oxide and (*S*)-(2*l*,6*l*,1'*u*)-6-Methyl-3-(1-methylethyl)-2-(1'-phenylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*l*)-30 and (*u*)-30). In an oven-dried, 100-mL, three-necked, round bottomed flask equipped with a N_2 inlet, stir bar, thermometer, and septum was placed *trans*-**9** (308 mg, 1.15 mmol) in anhydrous THF (50 mL). The solution was cooled to an internal temperature of −72 °C. To this solution was added *t*-BuLi (1.58 M in pentane; 729 μL, 1.15 mmol, 1.0 equiv) with the formation of a pale yellow color. The mixture was stirred for 30 min, and methyl iodide (358 μL, 5.76 mmol, 5.0 equiv) was added. The color dissipated in about 30 s. The mixture was stirred for 30 min and H_2O (3 mL) was added. After the reaction mixture had warmed to rt, THF was removed under reduced pressure. H_2O (10 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated to afford a white solid. HPLC analysis showed a ratio of 5.8/1 (*l*/*u*). The crude product was purified by MPLC (EtOAc/*i*-PrOH, 99/1) to afford 279 mg (86%) of (*l*)-**30** and 50 mg (14%) of (*u*)-**30**. Analytical samples were obtained by recrystallization from hexane. Data for (*l*)-**30**: mp 107.5−108.3 °C (hexane); ^{1}H NMR (300 MHz) 7.36−7.20 (m, 5H, Ph), 4.09−3.90 (m, 2H, HC(6), $(CH_3)_2CHN$), 3.24 (dq, J_{HP} = 18.4, J_{HH} = 7.4, 1H, HC(1')), 3.10−2.98 (m, 1H, $H_{eq}C(4)$), 2.67−2.57 (m, 1H, $H_{ax}C(4)$), 1.61(dd, J_{HP} = 17.2, J_{HH} = 7.4, 3H, $H_3C(2')$), 1.61−1.40 (m, 2H, $H_2C(5)$), 1.22 (d, J = 6.2, 3H, $H_3C(7)$), 1.18(d, J = 6.6, 3H, $H_3C(9)$), 1.13(d, J = 6.8, 3H, H_3C-(9)); ^{13}C NMR (75.5 MHz) 139.3 (J = 6.8, C_{ipso}), 128.2 (J = 6.0, C_{ortho}), 127.9 (J = 2.0, C_{para}), 126.2 (J = 3.0, C_{meta}), 76.0 (J = 8.6, C(6)), 46.0 (J = 3.7, $(CH_3)_2CHN$), 39.1 (J = 123.7, C(1')), 37.7 (J = 1.7, C(4)), 33.6 (J = 7.2, C(5)), 22.2 (J = 5.3, C(7)), 21.3 (C(9)), 20.1 (J = 4.7, C(9)), 15.6 (J = 4.7, C(2')); ^{31}P NMR (121.65 MHz) 25.35; IR (CCl_4) 3028 (w), 2975 (s), 1254 (s, P=O); MS (70 eV) 281 (M^+, 3), 134 (100); TLC R_f 0.44 (EtOAc/*i*-PrOH, 49/1); HPLC t_R 8.64 min (Supelco LC-Si, EtOAc/*i*-PrOH, 24/1, 1.0 mL/min); $[\alpha]_D$ −78.88° (CH_2Cl_2, c = 1.61). Anal. Calcd for $C_{15}H_{24}NO_2P$ (281.32): C, 64.04; H, 8.60; N, 4.98; P, 11.01. Found: C, 64.24; H, 8.62; N, 4.99; P, 10.94. Data for (*u*,*u*)-**30**: mp 88−90.2 °C (hexane); ^{1}H NMR (300 MHz) 7.42−7.20 (m, 5H, Ph), 4.24−4.12 (m, 1H, HC(6)), 3.68−3.56 (m, 1H, $(CH_3)_2CHN$), 3.25 (dq, J_{HP} = 17.7, J_{HH} = 7.3, 1H, HC(1')), 3.1−2.97 (m, 1H, $H_{eq}C(4)$), 2.88−2.78 (m, 1H, $H_{ax}C(4)$), 1.58 (dd, J_{HP} = 17.1, J_{HH} = 7.3, 3H, $H_3C(2')$), 1.69−1.56 (m, 2H, $H_2C(5)$), 1.35 (dd, J_{HH} = 6.0, J_{HP} = 1.2, 3H, $H_3C(7)$), 1.02 (d, J = 6.6, 3H, $H_3C(9)$), 0.46 (d, J = 6.7, 3H, $H_3C(9)$); ^{31}P NMR (121.65 MHz) 26.56; MS (70 ev) 281 (M^+, 3), 134 (100); High-resolution MS calcd for $C_{15}H_{24}NO_2P$ 281.1545, found 281.1544; TLC R_f 0.54 (EtOAc/*i*-PrOH, 49/1); HPLC t_R 6.03 min (Supelco LC-Si, EtOAc/*i*-PrOH, 24/1, 1.0 mL/min).

(*S*)-(2*u*,6*l*,1'*l*)-6-Methyl-3-(1-methylethyl)-2-(1'-phenylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*l*)-32). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed *trans*-**16** (107 mg, 0.38 mmol) in anhydrous THF (3.8 mL). The solution was cooled to −78 °C and *t*-BuLi (2.19 M in pentane, 189 μL, 0.41 mmol, 1.1 equiv) was added. The resulting yellowish solution was stirred at this temperature for 10 min. Anhydrous methyl iodide (70 μL, 1.13 mmol, 3 equiv) was added with instant color dissipation. The reaction mixture was stirred for 10 min followed by addition of H_2O (5 mL). The resulting slurry was gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 44.3/1 (*l*/*u*). The residual oil was purified by SiO_2 column chromatography (benzene) to yield 108 mg (97%) of (*l*)-**21** as a white solid. An analytical sample was obtained by recrystallization from Et_2O/hexane: mp 157−158 °C (Et_2O/hexane); ^{1}H NMR (400 MHz) 7.40−7.21 (m, 5H, Ph), 4.45−4.35 (m, 2H, HC(6), $(CH_3)_2CHN$), 3.61 (dq, J_{HP} = 14.4, J_{HH} = 7.1, 1H, HC-(1')), 3.22 (ddt, J_{HP} = 17.9, J_{HH} = 13.8, 3.8, 1H, $H_{eq}C(4)$), 2.99−2.91 (m, 1H, $H_{ax}C(4)$), 1.70−1.60 (m, 2H, $H_2C(5)$), 1.56 (dd, J_{HP} = 20.3, J_{HH} = 7.2, J_{HH} = 7.2, 3H, $H_3C(2')$), 1.23 (dd, J_{HH} = 6.1, J_{HP} = 1.5, 3H, $H_3CC(6)$), 1.16 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_b$CHN), 1.12 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_b$CHN); ^{13}C NMR (100 MHz) 139.0 (J = 5.4, C_{ipso}), 128.6 (J = 5.9, C_{ortho}), 128.0 (J = 2.6, C_{meta}), 126.6 (J = 3.1, C_{para}), 75.7 (J = 9.7, C(6)), 48.1 (J = 4.8, $(CH_3)_2CHN$), 41.4 (J = 87.3, C(1')), 38.2 (C(4)), 34.4 (J = 6.5, C(5)), 22.6 (J = 6.9, $CH_3C(6)$), 21.4 ($(CH_3)_a(CH_3)_b$CHN), 20.4 (J = 5.4, $(CH_3)_a(CH_3)_b$CHN), 16.82 (C(2')); ^{31}P NMR (161.9 MHz) 91.57; IR ($CHCl_3$) 3025 (m), 2979 (s), 1229 (w); MS (70 eV) 297 (M^+, 4), 192 (100); TLC R_f 0.26 (hexane/EtOAc, 6/1); $[\alpha]_D$ −140.95° (c = 0.53, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}NOPS$ (297.40): C, 60.58; H, 8.13; N, 4.71; P, 10.41; S, 10.78. Found: C, 60.60; H, 8.16; N, 4.71; P, 10.32; S, 10.75.

(*S*)-(2*u*,6*l*,1'*l*)-2-(1',2'-Diphenylethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide and (*S*)-(2*u*,6*l*,1'*u*)-2-(1',2'-Diphenylethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*l*)-33 and (*u*)-33). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed *trans*-**16** (120 mg, 0.423 mmol) in anhydrous THF (4.2 mL). The solution was cooled to −78 °C, and *t*-BuLi (2.19 M in pentane, 213 μL, 0.47 mmol, 1.1 equiv) was added. The resulting yellowish solution was stirred at this temperature for 10 min. Anhydrous benzyl bromide (151 μL, 1.27 mmol, 3.0 equiv) was added with instant color dissipation. The reaction mixture was stirred for 2 h followed by addition of H_2O (5 mL). The resulting slurrish mixture was gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 15.6/1 (*l*/*u*). The residual oil was purified by SiO_2 column chromatography (petroleum ether/Et_2O, 4/1) to yield 141 mg (89%) of (*l*)-**33** and 9 mg (6%) of (*u*)-**33**. An analytical sample of (*l*)-**33** was obtained by Kugelrohr distillation. Data for (*l*)-**33**: bp 145 °C (10^{-4} Torr, air bath); ^{1}H NMR (400 MHz) 7.35−6.91 (m, 10H, Ar), 4.49 (dsept, J_{HP} = 20.0, J_{HH} = 6.6, 1H, $(CH_3)_2CHN$), 4.38−4.29 (m, 1H, HC(6)), 3.66 (ddd, J = 15.9,

11.4, 1.7, 1H, $H_aH_bC(2')$), 3.38−3.19 (m, 3H, $H_{eq}C(4)$, $H_{ax}C(4)$, HC(7')), 3.03 (ddd, J = 14.2, 10.4, 3.9, 1H, $H_aH_bC(2')$), 1.68−1.59 (m, 2H, $H_2C(5)$), 1.19 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 1.15 (d, J = 4.9, 3H, $H_3CC(6)$), 1.15 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (100 MHz) 139.4 (J = 18.3, C_{ipso}), 136.2 (J = 5.3, $C_{ipso'}$), 129.2(J = 6.1, C_{ortho}), 128.4 ($C_{ortho'}$), 127.9 ($C_{meta'}$), 127.9 (J = 2.3, C_{meta}), 126.6 (J = 3.1, C_{para}), 125.8 ($C_{para'}$), 75.6 (J = 9.2, HC(6)), 49.6 (J = 86.2, HC(1')), 48.1 (J = 4.6, $(CH_3)_2CHN$), 38.1 (C(4)), 37.6 (J = 2.3, C(2')), 34.4 (J = 6.1, C(5)), 22.5 (J = 6.9, $CH_3C(6)$), 21.4 ($(CH_3)_a(CH_3)_b$-CHN), 20.5 (J = 5.3, $((CH_3)_a(CH_3)_bCHN$); ^{31}P NMR (161.9 MHz) 89.07; IR ($CHCl_3$) 3086 (w), 2978 (s), 1265 (m); MS (70 eV) 373 (M^+, 2) 160 (100); TLC R_f 0.35 (petroleum ether/Et_2O, 4/1); $[\alpha]_D$ −8.22° ($CHCl_3$, c = 2.97). Anal. Calcd for $C_{21}H_{28}NOPS$ (373.48): C, 67.53; H, 7.56; N, 3.75; P, 8.29; S, 8.58. Found: C, 67.55; H, 7.58; N, 3.73; P, 8.24; S, 8.50. Data for (*u*)-**33**: ^1H NMR (400 MHz) 7.43−7.03 (m, 10H, Ar), 4.37−4.26 (m, 1H, C(6)), 3.91 (dsept, J_{HP} = 20.0, 6.8, 1H, $(CH_3)_2CHN$), 3.74 (ddd, J_{HP} = 17.1, J_{HH} = 9.3, 4.6, 1H, HC(1')), 3.46 (ddd, J_{HH} = 14.2, J_{HP} = 12.2, J_{HH} = 4.8, 1H, HaHbC(2')), 3.25 (ddd, J_{HH} = 14.2, J_{HP} = 13.4, J_{HH} = 9.3, 1H, HaHbC(2')), 3.14−2.97 (m, 2H, $H_2C(4)$), 1.72−1.58 (m, 2H, $H_2C(5)$), 1.27 (d, J_{HH} = 6.2, J_{HP} = 1.6, 3H, $H_3CC(6)$), 0.97 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_b$-CHN), 0.15 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{31}P NMR (161.9 MHz) 90.16; MS (70 eV) 373 (M^+, 2), 160 (100); High-resolution MS calcd for $C_{21}H_{28}NOPS$ 373.1629, found: 373.1628; TLC R_f 0.42 (petroleum ether/Et_2O, 4/1).

(*S*)-(2*u*,6*l*,1'*u*)-6-Methyl-3-(1-methylethyl)-2-(1'-methylpentyl)-1,3,2-oxazaphosphorinane 2-Sulfide and (*S*)-(2*u*,6*l*,1'*l*)-6-Methyl-3-(1-methylethyl)-2-(1'-methylpentyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*u*)-34 and (*l*)-34). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed *trans*-**17** (100 mg, 0.45 mmol) in anhydrous THF (2.3 mL). The solution was cooled to −78 °C and *n*-BuLi (2.75 M in hexane, 173 μL, 0.48 mmol, 1.05 equiv) was added. The resulting yellowish solution was stirred at this temperature for 60 min. Anhydrous *n*-butyl iodide (155 μL, 1.36 mmol, 3.0 equiv) was added over 30 s. The reaction mixture was stirred for 7 h followed by addition of H_2O (5 mL). The resulting slurry was gradually warmed to rt. The aqueous layer was separated and extracted with TBME (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 12.6/1 (*u*/*l*). The residual oil was purified by SiO_2 column chromatography (hexane/EtOAc, 8/1) to yield 110 mg (87%) of **34** as a colorless oil. An analytical sample of **34** was obtained by Kugelrohr distillation. Data for (*u*)-**34** and (*l*)-**34**: bp 95 °C (0.1 Torr, air bath); ^1H NMR (400 MHz) 4.39 (dsept, J_{HP} = 20.0, J_{HH} = 6.6, 1H, $(CH_3)_2CHN$), 4.36−4.27 (m, 1H, HC(6)), 3.25 (ddt, J_{HP} = 18.3, J_{HH} = 14.2, 4.2, 1H, $H_{eq}C(4)$), 3.05 (ddd, J = 14.6, 11.0, 3.9, 1H, $H_{ax}C(4)$), 2.34−2.22 (m, 1H, HC(1')), 1.71−1.64 (m, 2H, $H_2C(5)$), 1.63−1.16 (m, 6H, $H_2C(2')$), $H_2C(3')$, $H_2C(4')$), 1.36 (dd, J_{HH} = 6.3, J_{HP} = 1.2, 3H, $CH_3C(6)$), 1.15 (dd, J_{HP} = 20.0, J_{HH} = 6.8, 3H, $CH_3CH(1')$), 1.14 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 1.07 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.89 (t, J = 7.2, 3H, $H_3C(5')$); ^{13}C NMR (100 MHz) for (*u*)-**34**: 74.6 (J = 8.4, C(6)), 47.8 (J = 4.6, $(CH_3)_2CHN$), 38.1 (C(4)), 34.6 (J = 6.1, C(5)), 31.2 (J = 93.08, C(1')), 29.5 (C(2')), 29.2 (J = 16.02, C(3')), 23.0 (J = 7.6, $CH_3C(6)$), 22.4 (C(4')), 21.7 $(CH_3)_a(CH_3)_bCHN$), 20.3 (J = 6.1, $(CH_3)_a(CH_3)_bCHN$), 13.8 (C(5')), 12.9 (J = 2.3, $CH_3C(1')$); ^{13}C NMR for (*l*)-**34**: 74.8 (J = 9.2, C(6)), 47.7 (J = 3.8, $(CH_3)_2CHN$), 38.0 (C(4)), 34.6 (J = 6.1, C(5)), 31.2 (J = 93.1, C(1')), 29.8 (C(2')), 29.4 (J = 16.0, C(3')), 23.0 (J = 7.6, $CH_3C(6)$), 22.5 (C(4')), 21.7 $((CH_3)_a(CH_3)_bCHN)$, 20.3 (J = 6.1, $(CH_3)_a(CH_3)_bCHN$), 13.8 (C(5')), 13.1 ($CH_3C(1')$); ^{31}P NMR (161.9 MHz) (*u*)-**34**: 97.65, (*l*)-**34**: 98.00; IR (neat) 2967 (s), 1173 (s); MS (70 eV) 277 (M^+, 12), 160 (100); TLC R_f 0.44 ((*u*)-**34**), 0.41 ((*l*)-**34**) (hexane/EtOAc, 8/1); $[\alpha]_D$ −63.8° ($CHCl_3$, c = 0.81). Anal. Calcd for $C_{13}H_{28}NOPS$ (277.41): C, 56.29; H, 10.17; N, 5.05; P, 11.17; S, 11.56. Found: C, 56.34; H, 10.15; N, 5.03; P, 11.08; S, 11.49.

(*S*)-(2*l*,6*l*,1'*l*)-6-Methyl-3-(1-methylethyl)-2-(1'-methylpentyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*l*)-21). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed diastereomerically pure (*u*)-**21** (64 mg, 0.22 mmol) in anhydrous THF (2.2 mL). The solution was cooled to −78 °C, and *t*-BuLi (2.19 M in pentane, 118 μL, 0.26 mmol, 1.2 equiv) was added. The resulting yellowish solution was stirred at this temperature for 1 h and at −20 °C for 10 min. A solution of acetic acid (37 μL, 0.65 mmol, 3.0 equiv) in anhydrous THF (650 μL) was added. The reaction mixture became colorless and then quenched with aqueous $NaHCO_3$ (saturated $NaHCO_3/H_2O$, 1/1, 5 mL). The aqueous layer was separated and extracted with TBME (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 17/83 (*u*/*l*). Column chromatographic purification (hexane/EtOAc, 8/1) of the residual oil on SiO_2 afforded 63 mg (98.3%) of **21** as a white solid. Recrystallization of **21** from hexane/Et_2O (3/1) led to the highly diastereomerically enriched (*l*)-**21**: mp 67−70 °C (pentane); ^1H NMR (300 MHz) 7.37−7.21 (m, 5H, Ph), 4.55−4.42 (m, 1H, HC(6)), 3.79−3.61 (m, 1H, $(CH_3)_2CHN$), 3.38 (dq, J_{HP} = 14.8, J_{HH} = 7.3, 1H, HC(1')), 3.09−2.93 (m, 1H, $H_{ax}C(4)$), 2.91−2.79 (m, 1H, $H_{eq}C(4)$), 1.87−1.78 (m, 1H, $H_{eq}C(5)$), 1.63 (dd, J_{HP} = 20.0, J_{HH} = 7.3, 3H, $H_3C(2')$), 1.49−1.36 (m, 1H, $H_{ax}C(5)$), 1.30 (dd, J_{HH} = 6.2, J_{HH} = 1.0, 3H, CH_3C-(6)), 1.12 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.82 (d, J = 6.8, $(CH_3)_a(CH_3)_bCHN$); ^{13}C NMR (75.5 MHz) 138.4 (J = 5.1, C_{ipso}), 129.0 (J = 6.1, C_{ortho}), 127.9 (J = 2.9, C_{meta}), 126.9 (J = 3.4, C_{para}), 70.1 (J = 7.6, C(6)), 47.7 (J = 4.8, $(CH_3)_2CHN$), 46.9 (J = 93.8, C(1')), 36.6 (C(4)), 33.8 (J = 2.9, C(5)), 22.1 (J = 8.7, $CH_3C(6)$), 20.3 (J = 7.3, $(CH_3)_a(CH_3)_bCHN$), 19.8 ($(CH_3)_a(CH_3)_bCHN$), 19.8 (C(2')); ^{31}P NMR (161.9 MHz) 96.00; IR ($CHCl_3$) 3023 (m), 2977 (s); MS (70 eV) 297 (M^+, 5), 192 (100); TLC R_f 0.47 (hexane/EtOAc, 8/1); $[\alpha]_D$ +52.9° ($CHCl_3$, c = 0.42). Anal. Calcd for $C_{15}H_{24}NOPS$ (297.39): C, 60.58; H, 8.13; N, 4.71; P, 10.41; S, 10.78. Found: C, 60.62; H, 8.14; N, 4.74; P, 10.38; S, 10.73.

(*S*)-(2*l*,6*l*,1'*l*)-2-(1',2'-Diphenylethyl)-3-(1-methylethyl)-6-methyl-1,3,2-oxazaphosphorinane 2-Sulfide ((*l*)-22). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed diastereomerically pure (*u*)-**22** (67 mg, 0.18 mmol) in anhydrous THF (1.8 mL). The solution was cooled to −78 °C, and *t*-BuLi (2.19 M in pentane, 98 μL, 0.21 mmol, 1.2 equiv) was added. The resulting yellowish solution was stirred at this temperature for 40 min and at −10 °C for 10 min. A solution of acetic acid (30.6 μL, 0.53 mmol, 3.0 equiv) in anhydrous THF (530 μL) was added. The reaction mixture became colorless and then quenched with aqueous $NaHCO_3$ (saturated $NaHCO_3/H_2O$, 1/1, 5 mL). The aqueous layer was separated and extracted with TBME (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 45/55 (*u*/*l*). Column chromatographic purification (hexane/EtOAc, 6/1) of the residual oil on SiO_2 afforded 66 mg (99.8%) of **22** as a white solid. Recrystallization of **22** from hexane led to the pure (*u*)-**22**. The filtrate was concentrated to give the highly diastereomerically enriched (*l*)-**22** as a colorless oil: ^1H NMR (300 MHz) 7.33−6.94 (m, 10H, Ar), 4.60−4.47 (m, 1H, HC(6)), 3.68 (dsept, J_{HP} = 18.5, J_{HH} = 6.7, 1H, $(CH_3)_2CHN$), 3.59 (ddd, J_{HH} = 13.3, J_{HP} = 10.1, J_{HH} = 3.0, 1H, HC(1')), 3.45 (ddd, J_{HP} = 18.2, J_{HH} = 11.5, 2.9, 1H, H_aH_bC-(2')), 3.22 (ddd, J_{HP} = 13.8, J_{HH} = 11.5, 7.3, 1H, $H_aH_bC(2')$), 3.13−2.89 (m, 2H, $H_2C(4)$), 1.94−1.84 (m, 1H, $H_{eq}C(5)$), 1.64−1.51 (m, 1H, $H_{ax}C(5)$), 1.33 (dd, J_{HH} = 6.2, J_{HH} = 1.0, 3H, $CH_3C(6)$), 1.11 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.69 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_b$-CHN); ^{31}P NMR (121.65 MHz) 94.40; MS (70 eV) 373 (M^+, 2) 160 (100); High-resolution MS calcd for $C_{21}H_{28}NOPS$ 373.1629, found 373.1624; TLC R_f 0.5 (benzene).

(*S*)-(2*u*,6*l*,1'*u*)-6-Methyl-3-(1-methylethyl)-2-(1'-phenylethyl)-1,3,2-oxazaphosphorinane 2-Sulfide ((*u*)-32). In a flame-dried, 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed diastereomerically pure oxazaphosphorinane 2-sulfide (*l*)-**32** (52 mg, 0.18 mmol) in anhydrous THF (1.8 mL). The solution was cooled to −78 °C, and *t*-BuLi (2.19 M in pentane, 96 μL, 0.21 mmol, 1.2 equiv) was added. The resulting yellowish solution was stirred at this temperature for 1 h and at −20 °C for 10 min. A solution of acetic acid (30 μL, 0.53 mmol, 3.0 equiv) in anhydrous THF (530 μL) was added. The reaction mixture became colorless and quenched with aqueous $NaHCO_3$ (saturated $NaHCO_3/H_2O$, 1/1, 5 mL). The aqueous layer was separated and extracted with TBME (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. ^{31}P NMR spectroscopic analysis of the crude products showed a diastereomeric ratio of 48/52 (*l*/*u*). Column chromatographic purifica-

tion (hexane/EtOAc, 6/1) of the residual oil on SiO_2 afforded 50 mg (99.8%) of **32** as a white solid. Recrystallization of **32** from hexane/Et_2O (3/1) led to the pure (*l*)-**32**. The filtrate was concentrated to give the highly diastereomerically enriched (*u*)-**32** as a colorless oil. Data for (*u*)-**32**: ^{1}H NMR (300 MHz) 7.40−7.20 (m, 5H, Ph), 4.45−4.34 (m, 1H, HC(6)), 3.92 (dsept, J_{HP} = 18.7, J_{HH} = 6.7, 1H, $(CH_3)_2CHN$), 3.68 (dq, J_{HP} = 14.3. J_{HH} = 7.1, 1H, HC(1′)), 3.22−3.02 (m, 2H, $H_2C(4)$), 1.76−1.62 (m, 2H, $H_2C(5)$), 1.58 (dd, J_{HP} = 19.7, J_{HH} = 7.1, 3H, $H_3C(2')$), 1.40 (dd, J_{HH} = 6.2, J_{HP} = 1.6, 3H, $H_3CC(6)$), 1.00 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 0.35 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_b$-CHN); ^{31}P NMR (121.65 MHz) 92.73; MS (70 eV) 297 (M^+, 4), 192 (100); High-resolution MS calcd for $C_{15}H_{24}NOPS$ 297.1317, found 297.1317; TLC R_f 0.26 (hexane/EtOAc, 6/1).

(*S*)-(2*u*,6*l*,1′*u*)-6-Methyl-3-(1-methylethyl)-2-(1′-phenylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*u*)-19). In a 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed a diastereomeric pure 2-thioxooxazaphosphorinane (*u*)-**21** (74 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (2.5 mL). The solution was cooled on ice and a solution of mCPBA (85%, 76 mg, 0.38 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (2.5 mL) was added using a cannula over 30 s with instant sulfur colloid precipitation. The resulting reaction mixture was stirred for 40 min and quenched with saturated $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. ^{31}P NMR spectroscopic analysis of the crude products showed 100% retention at the phosphorus center and a single diastereomer (δ = 29.05). Column chromatographic purification (EtOAc/*i*-PrOH, 19/1) of the crude residue on SiO_2 yielded 71 mg (100%) of (*u*)-**19** as a white solid.

(*S*)-(2*l*,6*l*,1′*l*)-6-Methyl-3-(1-methylethyl)-2-(1′-phenylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*l*)-30). In a 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed a diastereomeric pure 2-thioxooxazaphosphorinane (*l*)-**32** (66 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (2.2 mL). The solution was cooled on ice and a solution of mCPBA (85%, 67 mg, 0.33 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (2.2 mL) was added using a cannula over 30 s with instant sulfur colloid precipitation. The resulting reaction mixture was stirred for 40 min and quenched with saturated $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. ^{31}P NMR spectroscopic analysis of the crude products showed 100% retention at the phosphorus center and a single diastereomer (δ = 27.5). Column chromatographic purification (EtOAc/*i*-PrOH, 49/1) of the crude residue on SiO_2 yielded 57 mg (92%) of (*l*)-**30** as a white solid.

(*R*)-Dimethyl (1-Phenylethyl)phosphonate ((*R*)-35). In a 25-mL round-bottomed flask fitted with a reflux condenser was placed (*u*)-**19** (120 mg, 0.43 mmol) in aqueous HCl (6 N, 18 mL). The resulting homogeneous solution was stirred at reflux for 14 h. The reaction mixture was concentrated and the residue purified by ion exchange chromatography (H_2O, 20 mm × 8 cm, AG 50W-X8) to give 73 mg of phosphonic acid. The amino alcohol hydrochloride salt **14**·HCl was eluted with 6 N HCl. The eluent was concentrated and redissolved in H_2O (2 mL). The solution was basicified with KOH pellets at 0 °C until the pH reached *ca.* 11. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated. The residual oil was purified by Kügelrohr distillation (75 °C, 10 Torr) to give 27 mg (48%) of **14** as a colorless oil.

In a 30-mL Pyrex tube was placed the phosphonic acid in anhydrous CH_3OH/Et_2O (5.5 mL, 1/10). The solution was cooled on ice, and freshly distilled CH_2N_2 in Et_2O was added until the solution stayed yellow. Excess of CH_2N_2 was quenched with a solution of acetic acid in Et_2O (1/20). The solution was concentrated, and the residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 49/1) to afford 85 mg (93%) of (*R*)-**35** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation: bp 95 °C (0.1 Torr, air bath); ^{1}H NMR (400 MHz) 7.38−7.24 (m, 5H, Ph), 3.69 (d, J_{HP} = 10.7, OCH_3), 3.53 (d, J_{HP} = 10.5, 3H, OCH_3), 3.22 (dq, J_{HP} = 22.5, J_{HH} = 7.4, 1H, HC(1)), 1.59 (dd, J_{HP} = 18.6, J_{HH} = 7.3, 3H, $CHCH_3Ph$); ^{31}P NMR (161.9 MHz) 32.75; TLC R_f 0.26 (EtOAc/*i*-PrOH, 49/1); $[\alpha]_D$ +2.9°; $[\alpha]_{405}$ +15.3° (CH_2Cl_2, *c* = 2.66).

(*S*)-Dimethyl (1-Phenylethyl)phosphonate ((*S*)-35). In a 25-mL round-bottomed flask fitted with a reflux condenser was placed oxazaphosphorinane 2-oxide (*l*)-**30** (100 mg, 0.35 mmol) in aqueous HCl (6 N, 15 mL). The resulting homogeneous solution was stirred at reflux for 14 h. The reaction mixture was concentrated, and the residue purified by ion exchange chromatography (H_2O, 20 mm × 8 cm, AG 50W-X8) to give 64 mg of phosphonic acid. The amino alcohol hydrochloride salt **14**·HCl was eluted with 6 N HCl. The eluent was concentrated and redissolved in H_2O (2 mL). The solution was basicified with KOH pellets at 0 °C until the pH reached *ca.* 11. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated. The residual oil was purified by Kügelrohr distillation (75 °C, 10 Torr) to give 25 mg (53%) of **14** as a colorless oil.

In a 30-mL Pyrex tube was placed the phosphonic acid in anhydrous Et_2O/CH_3OH (5.5 mL, 10/1). The solution was cooled on ice, and freshly distilled CH_2N_2 in Et_2O was added until the solution stayed yellow. Excess of CH_2N_2 was quenched with a solution of acetic acid in Et_2O (1/20). The solution was concentrated, and the residual oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 49/1) to afford 73 mg (95.4%) of (*S*)-**35** as a colorless oil. An analytical sample was obtained by Kugelrohr distillation: bp 95 °C (0.1 Torr, air bath); ^{1}H NMR (400 MHz) 7.38−7.24 (m, 5H, Ph), 3.69 (d, J_{HP} = 10.5, 3H, OCH_3), 3.53 (d, J_{HP} = 10.5, 3H, OCH_3), 3.22 (dq, J_{HP} = 22.5, J_{HH} = 7.5, 1H, HC(1)), 1.59 (dd, J_{HP} = 18.6, J_{HH} = 7.3, 3H, $CHCH_3Ph$); ^{31}P NMR (161.9 MHz) 32.76; TLC R_f 0.26 (EtOAc/*i*-PrOH, 49/1); $[\alpha]_D$ −3.73°; $[\alpha]_{405}$ −18.1° (*c* = 2.36, CH_2Cl_2).

(*S*)-(2*u*,6*l*,1′*u*)-2-(1′-Methoxyethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*u*)-27). In a 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed a diastereomeric mixture of (*u*)-**29** and (*l*)-**29** (ds = 15.6/1, 31 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (2 mL). The solution was cooled on ice, and a solution of mCPBA (85%, 37 mg, 0.19 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (1 mL) was added using a cannula over 30 s with instant sulfur colloid precipitation. The resulting reaction mixture was stirred for 45 min and quenched with saturated $NaHCO_3$ (3 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. ^{31}P NMR spectroscopic analysis of the crude products showed 100% retention at the phosphorus center and a diastereomeric ratio of 96.5/3.5 (*u*/*l*). Column chromatographic purification (EtOAc/*i*-PrOH, 24/1) of the residual oil on SiO_2 yielded 29 mg (100%) of (*u*)-**27** as a colorless oil: ^{1}H NMR (400 MHz) 4.48 (dqd, J = 12.7, 6.2, 2.7, 1H, HC(6)), 3.98−3.86 (m, 1H, $(CH_3)_2CHN$), 3.51 (dq, J = 7.0, 6.8, 1H, HC(1′)), 3.41 (d, J_{HP} = 0.5, 3H, OCH_3), 3.13−3.03 (m, 2H, $H_2C(4)$), 1.89−1.79 (m, 2H, $H_2C(5)$), 1.37 (dd, J_{HP} = 16.4, J_{HP} = 6.8, 3H, $H_3C(2')$), 1.30 (dd, J_{HH} = 6.3, J_{HP} = 1.5, 3H, $H_3C(6)$), 1.21 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_bCHN$), 1.12 (d, J = 6.8, 3H, $(CH_3)_a(CH_3)_b$-CHN); ^{31}P NMR (161.9 MHz) for (*u*)-**27**: 23.44; ^{31}P NMR for (*l*)-**27**: 24.72; TLC R_f 0.3 (EtOAc/*i*-PrOH, 49/1).

(*S*)-(2*u*,6*l*,1′*l*)-2-(1′-Methoxyethyl)-6-methyl-3-(1-methylethyl)-1,3,2-oxazaphosphorinane 2-Oxide ((*l*)-27). In a 25-mL, two-necked, round-bottomed flask fitted with a N_2 inlet and septum was placed a diastereomeric mixture of 2-thioxooxazaphosphorinanes (*u*)-**29** and (*l*)-**29** (ds = 1/11.1, 73 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (2mL). The solution was cooled on ice, and a solution of mCPBA (85%, 88 mg, 0.43 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (3.7 mL) was added using a cannula over 30 s with instant sulfur colloid precipitation. The resulting reaction mixture was stirred for 45 min and quenched with saturated $NaHCO_3$ (3 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. ^{31}P NMR spectroscopic analysis of the crude products showed 100% retention at the phosphorus center and a diastereomeric ratio of 8.8/91.2 (*u*/*l*). Column chromatographic purification (EtOAc/*i*-PrOH, 24/1) of the residual oil on SiO_2 yielded 67 mg (98.7%) of (*l*)-**27** as a colorless oil: ^{1}H NMR (400 MHz) 4.49−4.41 (m, 1H, HC(6)), 3.92 (dsept, J_{HP} = 20.0, J_{HH} = 6.6, 1H, $(CH_3)_2CHN$), 3.49 (dq, J_{HP} = 9.0, J_{HH} = 7.1, 1H, HC(1′)), 3.40 (d, J_{HP} = 0.7, 3H, OCH_3), 3.06−3.01 (m, 2H, $H_2C(4)$), 1.88−1.76 (m, 2H, $H_2C(5)$), 1.34 (dd, J_{HP} = 17.0, J_{HH} = 7.0, 3H, $H_3C(2')$), 1.28 (dd, J_{HH} = 6.1, J_{HP} = 1.5, 3H, $H_3CC(6)$), 1.17 (d, J = 6.6, 3H, $(CH_3)_a(CH_3)_b$-

CHN), 1.11 (d, $J = 6.8$, 3H, $(CH_3)_a(CH_3)_bCHN$); ^{31}P NMR (161.9 MHz) for (*u*)-**27**: 23.45; ^{31}P NMR for (*l*)-**27**: 24.69; TLC R_f 0.3 (EtOAc/*i*-PrOH, 49/1).

(*R*)-Dimethyl (1-Hydroxyethyl)phosphonate (37) and Dimethyl (1-Methoxyethyl)phosphonate (36). In an oven-dried NMR tube was introduced a diastereomeric mixture of (*u*)-**27** and (*l*)-**27** (ds = 71/29, 80 mg, 0.34 mmol) in anhydrous $CDCl_3$ (0.7 mL). The solution was cooled to −40 °C and treated with a solution of iodotrimethylsilane (242 μL, 1.71 mmol, 5 equiv) in anhydrous $CDCl_3$ (0.7 mL). The NMR tube was sealed, and the reaction mixture was warmed to rt. The reaction progress was monitored by ^1H and ^{13}C NMR spectroscopies, and the diagnostic C(6) signal disappeared in 4.5 h. The reaction mixture was allowed to stand at rt for 2 d to effect partial demethylation and concentrated *in vacuo*. The brownish residue was dissolved in acetone (3 mL) and treated with aqueous HCl (6 N, 570 μL, 3.4 mmol, 10 equiv). The solution was stirred for 24 h and concentrated under reduced pressure. The brownish oil dissolved in CH_3OH (1 mL) was purified by ion exchange chromatography (H_2O, 20 mm × 9 cm, AG 50W-X8). In a 50-mL Pyrex tube were placed the purified phosphonic acids in CH_3OH/Et_2O (1/6, 10 mL). The solution was cooled on ice and treated with freshly distilled CH_2N_2 in Et_2O until a yellow solution was obtained. Excess of CH_2N_2 was quenched with a solution of HOAc in Et_2O (1/20). The colorless solution was evaporated, and the residual yellowish oil was purified by SiO_2 column chromatography (EtOAc/*i*-PrOH, 24/1) to afford 38 mg (67%) of **36** and 10 mg (19%) of (*R*)-**37**. An analytical sample of **37** was obtained by Kugelrohr distillation. Data for (*R*)-**37**: bp 100 °C (0.1 Torr, air bath); ^1H NMR (400 MHz) 4.08−4.07 (m, 1H, HC(1)), 3.92−3.91 (bs, 1H, OH), 3.81 (d, $J_{HP} = 10.3$, 3H, $P(O)OCH_3$), 3.80 (d, $J_{HP} = 10.3$, 3H, $P(O)OCH_3$), 1.44 (dd, $J_{HP} = 17.6$, $J_{HH} = 7.1$, 3H, $H_3C(2)$); ^{31}P NMR (161.9 MHz) 28.52; MS (70 eV) 110 ($M - CH_3C(O)H^+$, 100); TLC R_f 0.12 (EtOAc/*i*-PrOH, 24/1); $[\alpha]_D$ −5.4° (acetone, $c = 0.50$), −2.83° (CH_3OH, $c = 0.50$). Data for **36**: ^1H NMR (300 MHz) 3.81 (d, $J = 10.4$, 3H, $P(O)OCH_3$), 3.80 (d, $J = 10.4$, $P(O)OCH_3$), 3.64 (quintet, $J_{HP} = J_{HH} = 7.1$, 1H, HC(1)), 3.48 (s, 3H, $C(1)OCH_3$), 1.40 (dd, $J_{HP} = 17.4$, $J_{HH} = 7.1$, 3H, $H_3C(2)$); ^{31}P NMR (161.9 MHz) 26.65; TLC R_f 0.2 (EtOAc/*i*-PrOH, 24/1).

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Supporting Information Available: Complete ^1H and ^{13}C NMR assignments along with complete listings of IR and MS data for all characterized compounds (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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