The Endocyclic Restriction Test: Investigation of the Geometries of Nucleophilic Substitution at Phosphorus(III) and Phosphorus(V)

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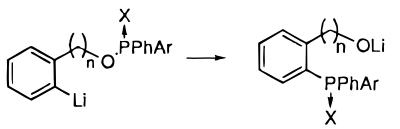
Abstract: Double labeling has been used under the endocyclic restriction test to show that transfers of phosphorus from oxygen to carbon in the conversions of lithio phosphinite **1** to alkoxy phosphine **8**, of lithio phosphinite **2** to alkoxy phosphine **9**, of lithio phosphinate **3** to alkoxy phosphine oxide **10**, and of lithio phosphinite borane **4** to alkoxy phosphine borane **11** proceed in an intramolecular fashion. The transfers of stereogenic phosphorus in the conversions of lithio phosphinite (*R*)-**5** to alkoxy phosphine (*R*)-**12**, of lithio phosphinate (*S*)-**6** to alkoxy phosphine oxide (*S*)-**13**, and of lithio phosphinite borane (*R*)-**7** to alkoxy phosphine borane (*R*)-**14** proceed with retention of stereochemistry at phosphorus. These results rule out the classic in-line S_N2 pathway and the geometrically equivalent in-line addition−elimination pathway for these endocyclic transfers of phosphorus. The most likely pathway for these nucleophilic substitutions at phosphorus is initial apical nucleophilic attack followed by pseudorotation and elimination of the apical alkoxy leaving group.

Introduction

Nucleophilic substitutions at stereogenic phosphorus(III) have been observed to take place with inversion of configuration at phosphorus in the majority of cases.[1−3] This inversion has been interpreted to show the reaction proceeds through a classic in-line S_N2 mechanism. A geometrically equivalent pathway is an in-line addition−elimination mechanism in which the first formed intermediate has the nucleophile and leaving group in apical positions. Loss of the apical leaving group affords inversion of configuration.[1i] Nucleophilic substitution at phosphorus(V) by carbon affords inversion of configuration in the majority of cases.[4−6] Both the in-line S_N2 mechanism and the in-line addition−elimination mechanism have been proposed. In a few cases the hydrolysis of phosphate esters with geometries constrained by a four-, five-, or six-membered ring have been observed to occur with a retention of configuration and been interpreted to proceed through a trigonal bipyramidal intermediate which undergoes a single Berry pseudorotation to achieve retention.[7]

In the present work the endocyclic restriction test has been used to evaluate the geometry of phosphorus transfer in the conversions of lithio phosphinite **1** to alkoxy phosphine **8**, lithio phosphinite **2** to alkoxy phosphine **9**, lithio phosphinate **3** to alkoxy phosphine oxide **10**, and lithio phosphinite borane **4** to alkoxy phosphine borane **11**.[8,9] The transfers of stereogenic phosphorus have been investigated for the conversions of lithio phosphinite **5** to alkoxy phosphine **12**, lithio phosphinate **6** to alkoxy phosphine oxide **13**, and lithio phosphinite borane **7** to alkoxy phosphine borane **14**. The results of these experiments allow us to rule out the in-line S_N2 mechanism and the in-line addition−elimination mechanism. We suggest an addition−pseudorotation-elimination pathway for the conversions of **1**−**7** to **8**−**14**, respectively.



1	**8** X=••, n=1, Ar=Ph
2	**9** X=••, n=2, Ar=Ph
3	**10** X=O, n=1, Ar=Ph
4	**11** X=BH_3, n=1, Ar=Ph
5	**12** X=••, n=2, Ar=β-Np
6	**13** X=O, n=2, Ar=β-Np
7	**14** X=BH_3, n=2, Ar=β-Np

In the endocyclic restriction test the geometry allowed for intramolecular transfer is restricted because the nucleophile and leaving group are linked by a tether.[9] In the conversions of **1**−**7** to **8**−**14**, respectively, the carbanion and alkoxy group are connected by varying length tethers in order to restrict the

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(1) For examples of inversion of configuration at phosphine centers see: (a) Smith, D. J. H.; Trippett, S. *J. Chem. Soc. Chem. Commun.* **1969**, 855. (b) Corfield, J. R.; Oram, R. K.; Smith D. J. H.; Trippett, S. *J. Chem. Soc. Perkin Trans. 1*, **1972**, 713. (c) Kyba, E. P. *J. Am. Chem. Soc.* **1975**, *97*, 2554. (d) Kyba, E. P. *J. Am. Chem. Soc.* **1976**, *98*, 4805. (e) Omelanczuk, J.; Mikolajczyk, M. *J. Chem. Soc. Chem. Commun.* **1976**, 1025. (f) Mikolajczyk, M.; Omelanczuk, J.; Perlikowska, W. *Tetrahedron* **1979**, *35*, 1531. (g) Mikolajczk, M. *Pure Appl. Chem.* **1980**, *52*, 959. (h) Nielsen, J.; Dahl, O. *J. Chem. Soc. Perkin Trans. 2* **1984**, 553. (i) Dahl. O. *Tetrahedron Lett.* **1981**, *22*, 3281. (j) Dahl, O. *Phosphorus and Sulfur* **1983**, *18*, 201.

(2) For examples of retention of configuration in nucleophilic attack in phosphines see: (a) Keglebich, G.; Quin, L. D. *Phosphorus and Sulfur* **1986**, *26*, 129. (b) Inch, T. D.; Hall, C. R. *Tetrahedron Lett.* **1976**, *40*, 3545.

(3) (a) Horner, J; Jordan, M. *Phosphorus and Sulfur* **1980**, *8*, 235. (b) Mosho, J. A. *Phosphorus and Sulfur* **1978**, *4*, 273.

(4) For examples of inversion in nucleophilic attack at phosphorus(V) see: (a) Korpiun, O.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 4784. (b) Lewis, R. A.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7009. (c) Van der Berg, G. R.; Plantenburg, D. H. J. M.; Benschop, H. P. *Recl. Trav. Chim.* **1972**, *91*, 929. (d) Cullis, P. M.; Kaye, A. D. *J. Chem. Soc. Chem. Commun.* **1992**, 346.

(5) For examples of retention and inversion of configuration at phosphorus(V) see: (a) Harrison, J. M.; Inch, T. D. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2885. (b) Haarger, M. J. P. *J. Chem. Soc. Perkin Trans. 1* **1977**, 2057.

(6) (a) Westheimer, F. H. *Acc. Chem Res.* **1968**, *1*, 70. (b) Hengge, A. C.; Edens, W. A.; Elsing, H. *J. Am. Chem. Soc.* **1995**, *116*, 5045. (c) Macomber, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 4386.

(7) (a) Rowell, R.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 5894. (b) DeBruin, K. E.; Zon, G.; Naumann, K.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7027.

(8) Li, J; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 9206.

(9) For a detailed review of the endocyclic restriction test, see: Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215.

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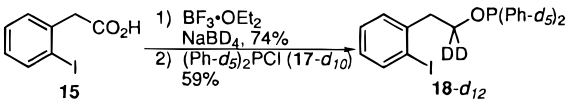
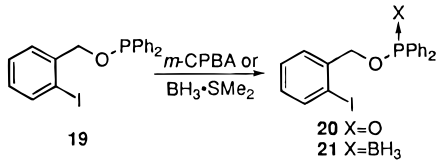
trajectory of intramolecular endocyclic nucleophilic attack at phosphorus. If the reaction pathway requires an in-line S_N2 transition state or a geometrically equivalent in-line addition−elimination intermediate, then the tether length needs to be sufficiently long to allow an angle of 180° between the nucleophile, phosphorus atom, and leaving group for intramolecular transfer to observed. In the case of the transition structure from the organolithium intermediates **1**−**7** intramolecular nucleophilic attack through a five- or six-membered endocyclic ring would not be possible for either in-line process and an intermolecular reaction would be expected. If intramolecular phosphorus transfer does take place a five- or six-membered endocyclic transition state or intermediate is required, and neither the classic in-line S_N2 mechanism nor the geometrically equivalent in-line addition−elimination mechanism can be the reaction pathway. In order to determine the molecularity of the reaction by double labeling experiments, **1**-d_{12}, **2**-d_{12}, **3**-d_{12}, and **4**-d_{12} were prepared.

Results

Syntheses of Phosphinite 18-d_{12}, Phosphinate 20-d_{12}, and Phosphinate Borane 21-d_7. Reduction of *o*-iodophenylacetic acid (**15**) with $NaBD_4$ and $BF_3{\cdot}OEt_2$ affords the labeled alcohol **16**-d_2 in good yield. Reaction with the labeled phosphinous chloride **20**-d_{10}[8] produced doubly labeled phosphinite **18**-d_{12}.

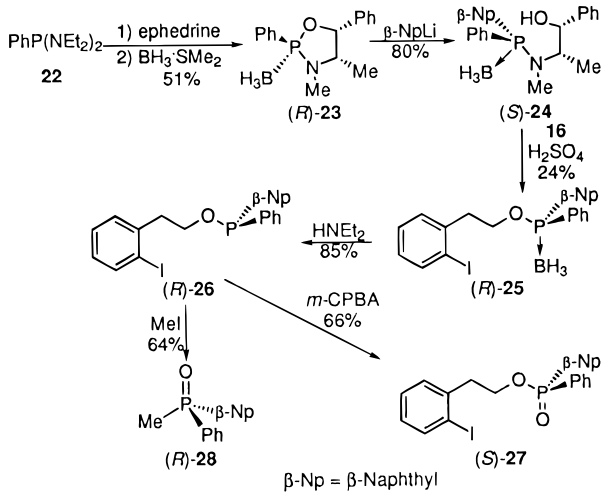


Phosphinates **20** and **20**-d_{12} were prepared by oxidation of the corresponding benzyl phosphinites **19** and **19**-d_{12} , respectively, with *m*-CPBA in excellent yields. Phosphinite borane **21** and **21**-d_7 were prepared by reaction of borane with phosphinites **19** and **19**-d_7.

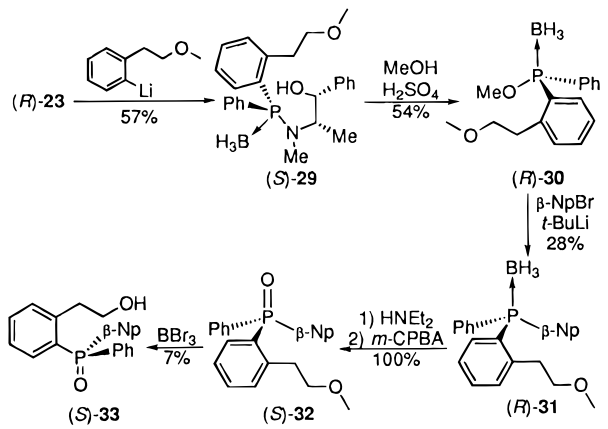


Syntheses of Chiral Phosphinite (*R*)-26, Phosphinate (*S*)-27, and Phosphinite Borane (*R*)-28. The requisite chiral phosphorus compounds were synthesized using (−)-ephedrine as a chiral auxiliary following the work of Juge.[10] Ephedrine was first reacted with bis(*N*,*N*-diethyl)phenylphosphinous diamide (**22**) and then complexed with borane to produce oxazaphospholidine borane (*R*)-**23** as one diastereomer.[11] Treatment of (*R*)-**24** with *β*-naphthyllithium yielded one diastereomer of aminophosphine borane (*S*)-**25** with retention of configuration at phosphorus assigned by analogy.[12] Acid catalyzed alcoholysis of (*S*)-**24** with *o*-iodophenethyl alcohol (**16**) produced chiral phosphinite borane (*R*)-**25** with inversion of stereochemistry at phosphorus.[13] Decomplexation of borane was achieved by treatment of (*R*)-**25** with diethylamine to afford phosphinite (*R*)-**26** with retention of stereochemistry at phosphorus.[14] Oxidation of (*R*)-**26** with *m*-CPBA gave phosphinate (*S*)-**27** with a retention of configuration at phosphorus assigned on the basis of the established stereochemical outcome of that reaction.[15]

The enantiomeric ratio (er) of phosphinite (*R*)-**26** was determined to be 89:11 (±5%) by conversion of (*R*)-**26** via the Arbuzov reaction to methylphenyl-naphthylphosphine oxide ((*R*)-**28**).[16] The Arbuzov reaction is known to proceed with full retention of stereochemistry at phosphorus.[1g] The enantiomeric ratio was determined by integration of the two peaks observed by ^{31}P NMR of a 1:1 mixture of (*R*)-**28** and *(S)*-(+)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine.[17] The absolute configuration of (*R*)-**28** was determined to be *R* by comparison of optical rotations to known values.[15] This configuration is as expected based on the stereochemical expectations for the steps of the synthesis.



Independent Synthesis of Phosphine Oxide (*S*)-33. The configurations at phosphorus of phosphine **37**, phosphine oxide **33**, and phosphine borane **39** derived from (*R*)-**26**, (*S*)-**27**, and (*R*)-**25**, respectively, were established independently by preparing phosphine oxide (*S*)-**33**. Addition of *o*-(methoxyethyl)-phenyllithium to oxazaphospholidine borane (*R*)-**23** afforded aminophosphine borane (*S*)-**29** as one diastereomer with retention.[12] Methanolysis of (*S*)-**29** gave phosphinite borane (*R*)-**30** with inversion at phosphorus.[13] Treatment of (*R*)-**30** with *β*-naphthyllithium gave the chiral tertiary phosphine borane (*R*)-**31** with inversion at phosphorus. Decomplexation of the borane and oxidation to the phosphine oxide (*S*)-**32** occurred with retention of configuration at phosphorus.[14,15] Finally, removal of the methyl group with boron tribromide provided alcohol (*S*)-**33**.



(10) Jugé, S.; Stephan, M. Laffitte, J. A.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357.

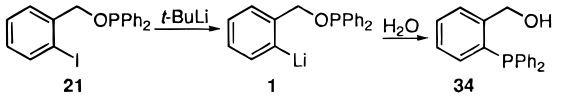
(11) The configuration of **(*R*)-19** has been established by X-ray crystallography: Jugé, S.; Stephans, M.; Genet, J. P.; Halut-Desportes, S.; Jeannin, S. *Acta Crystallogr., Sect. C* **1990**, *46*, 1869.

(12) The stereochemical outcome of organolithium addition to **(*R*)-19** has been established for the methyl and *o*-anisyl addition products by X-ray crystallography: Jugé, S.; Stephans, M.; Merdès, R.; Genet, J. P.; Halut-Desportes, S. *J. Chem. Soc. Chem. Commun.* **1993**, 531.

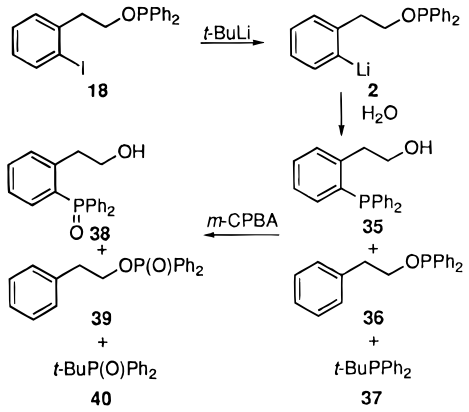
(13) The methanolysis of aminophosphine boranes is reported to occur with inversion of configuration.[10]

Transfers of Phosphorus: Reactions of Phosphinite 19, Phosphinite 18, Phosphinate 20, and Phosphinite Borane 21 with *t*-BuLi. Lithium−halogen exchanges of phosphinite **19**, phosphinite **18**, phosphinate **20**, and phosphinite borane **21** generated organolithium intermediates **1**−**4**, respectively, which after transfer of phosphorus from oxygen to carbon afford the alkoxy intermediates **8**−**11**, respectively. After addition of water and in some cases oxidation of phosphorus, the products were isolated and identified.

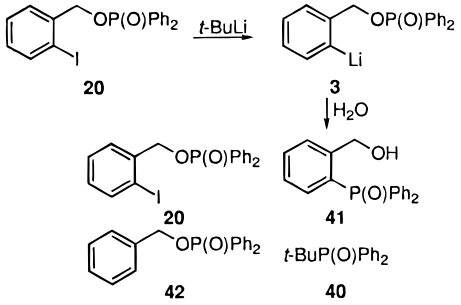
Previously we examined the transfer of phosphorus in the conversion of lithio phosphinite **1** to alkoxy phosphine **8**.[8] The transfer was found to afford phosphine **34** resulting from transfer of phosphorus from organolithium **1** to alkoxide **8**. Double labeling experiments established that the transfer of phosphorus in the conversion of **1** to **8** occurred intramolecularly.



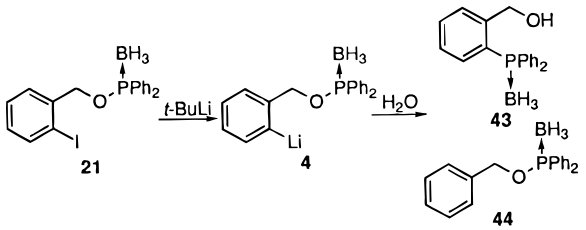
The aryllithium **2** was formed when a solution of 0.1 M phosphinite **18** dissolved in THF was treated with 2.0 equiv of *tert*-butyllithium. After 1 min the reaction was quenched with methanol and subsequently oxidized with *m*-CPBA to provide the corresponding phosphine oxides. The products observed were (*o*-(2-hydroxyethyl)phenyl)diphenylphosphine oxide (**38**, 43%), phenethyl diphenylphosphinate (**39**, 41%) and *tert*-butyldiphenylphosphine oxide (**40**, 16%). The *tert*-butyl addition product **40** is a result of the nucleophilic addition from *tert*-butyllithium while phosphinate **39** results from protonation of **2**. The (*o*-(2-hydroxyethyl)phenyl)diphenylphosphine oxide (**38**) which results from the transfer of phosphorus from oxygen to carbon in the conversion of aryllithium **2** to alkoxide **9** is the product of interest.



The transfer of phosphorus in the conversion of **3** to **10** was carried out when a 0.1 M solution of phosphinate **20** in THF was treated with 2.0 equiv of *tert*-butyllithium. After 1 min the reaction was quenched with water, and the products were isolated. The products observed were phosphine oxide **41** (85%), phenethyl diphenylphosphinate **42** (8%), *tert*-butyldiphenylphosphine oxide (**40**, 2%), and phosphinate **20** (5%). Triarylphosphine oxide **41** arises from transfer of phosphorus from oxygen to oxygen in the conversion of organolithium **3** to alkoxide **10**. The *tert*-butylphosphine oxide **40** results from addition of *tert*-butyllithium at phosphorus. Phosphinate **42** arises from protonation of **3**.



The transfer of phosphorus in the conversion of **4** to **11** a 0.1 M solution of phosphinite borane **21** in THF was treated with 2.0 equiv *tert*-butyllithium. After 1 min the reaction was quenched with methanol, and the products were isolated. Two products observed were the phosphine borane **43** (85%) and the phosphinite borane **44** (15%). Phosphine borane **43** arises from the transfer of phosphorus from **4** to **11**, while phosphinite borane **44** arises from protonation of **4**.



Transfers of Phosphorus: The Endocyclic Restriction Test of Phosphinite 18, Phosphinate 20, and Phosphinite Borane 21. Double labeling experiments were carried out to distinguish between the intermolecular and intramolecular pathways for the transfer of phosphorus from oxygen to carbon. The doubly labeled material had deuterium labels attached to the phosphorus phenyl rings and to the tether at the phenethyl position. A mixture of doubly labeled substrate and unlabeled substrate would produce a statistical mixture of doubly labeled, unlabeled, and singly labeled products from an intermolecular process while products from an intramolecular reaction would contain only doubly labeled and unlabeled materials.

A mixture of **18** and **18**-d_{12} was prepared as a 0.15 M THF solution, and its isotopic ratio was determined by FIMS (see Table 1). The phosphinite solution of **18** and **18**-d_{12} was treated with 2 equiv of *tert*-butyllithium to give organolithium intermediate **2** followed by transfer of the phosphorus atom to provide the alkoxy phosphine **9**. Treatment with water afforded phosphine **35** as a mixture of labeled and unlabeled materials. The isotopic composition of the product mixture as determined by FIMS is presented in Table 1. Comparison of the isotopic composition of **35** with the expected isotopic compositions for intramolecular and intermolecular processes establishes that the transfer of phosphorus in the conversion of phosphinite **18** to phosphine **35** occurs in an intramolecular fashion. Intermolecular products were <5% as indicated by the d_2 and d_{10} isotopic composition of the product **35**.

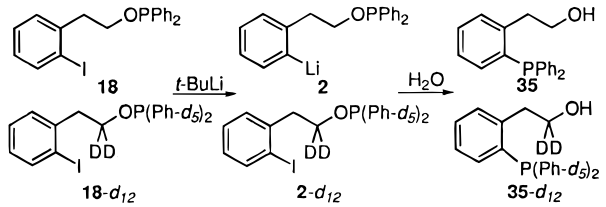
The transfer of phosphorus in the conversion of lithio phosphinate **3** to alkoxy phosphine oxide **10** was examined by a double labeling experiment in order to compare the transfer of phosphorus(V) to phosphorus(III). A mixture of **20** and **20**-d_{12} was prepared as a 0.01 M THF solution and its isotopic ratio was determined by FABMS (see Table 2). Treatment of the phosphinate mixture of **20** and **20**-d_{12} with 2 equiv of *tert*-

(14) Imamoto, T.; Kusumoto, T.; Suzuki, N.; Sato, K. *J. Am. Chem. Soc.* **1985**, *107*, 5301.
(15) Skowronska, A. *Bull. De L'Academie Polanaise Des Sciences* **1973**, *21*, 459.
(16) Korpiun, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842.
(17) Dunach, E.; Kagen, H. B. *Tetrahedron Lett.* **1985**, *26*, 2649.

Table 1. Isotopic Ratios for Phosphine Mixture **35** from the Double Label Experiment Using Phosphinite Mixture **18**[a]

	M	*M* + 1	*M* + 2	*M* + 10	*M* + 11	*M* + 12
reactant **18**[b]	54	1	0	1	8	35
product **35**	58	0	5	3	4	28
intramolecular[c]	54	1	0	1	8	35
intermolecular[c]	30	5	19	24	4	15

[a] Determined by FIMS (error ±5%). [b] A mixture of **18** and **18**-d_{12} with minor amounts of **18**-d_{11}. [c] Calculated based on the isotopic ratios of the starting materials.

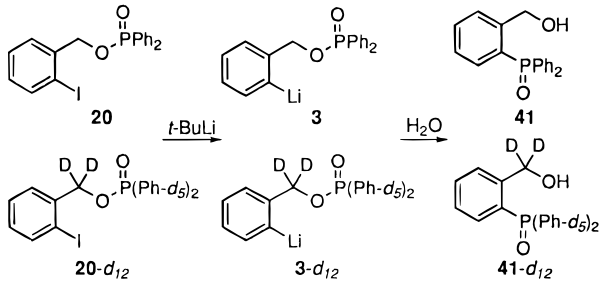


butyllithium produced organolithium **3** as a precursor to alkoxy phosphine oxide **10** which upon treatment with water afforded phosphine oxide **41**. The product mixture was analyzed by FABMS as presented in Table 2. Comparison of experimentally observed values with the calculated isotopic compositions for intramolecular and intermolecular reactions show the transfer of phosphorus(V) in the conversion of **3** to **10** occurred in an intramolecular fashion.

Table 2. Isotopic Ratios for Phosphine Oxide Mixture **41** from the Double Label Experiment using Phosphinate Mixture **20**[a]

	M	*M* + 1	*M* + 2	*M* + 10	*M* + 11	*M* + 12
reactant **20**[b]	47	0	0	2	9	41
product **41**	41	0	4	0	16	42
intramolecular[c]	47	0	0	2	9	41
intermolecular[c]	24	4	20	25	5	22

[a] Determined by FABMS (error ±5%). [b] A mixture of **20** and **20**-d_{12} with minor amounts of **20**-d_{10} and **22**-d_{11} materials [c] Calculated based on the isotopic ratios of the starting materials.

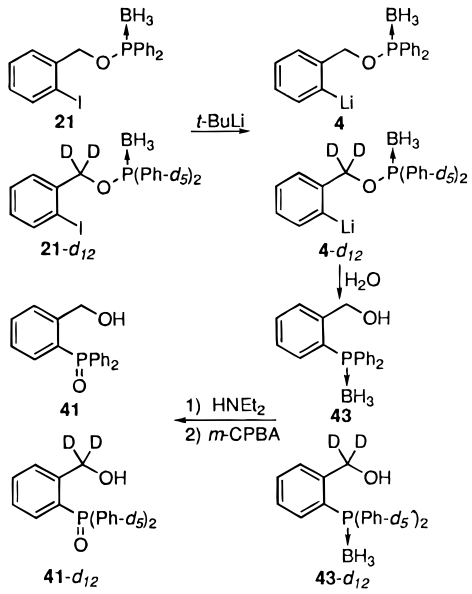


The molecularity of the transfer of a borane complexed phosphorus atom in the conversion of lithio phosphinite borane **4** to alkoxy phosphine borane **11** was also investigated by a double label experiment. A mixture of **21** and **21**-d_7 was prepared as a 0.10 M THF solution and its isotopic composition determined by FABMS (Table 3). The solution was treated with 2 equiv of *tert*-butyllithium to produce organolithium **4** as a precursor to alkoxide **11** which upon treatment with water afforded phosphinite borane **43.** In order to provide a reliable deuterium analysis phosphinite borane **43** was converted to phosphine oxide **41** by treatment of **43** with diethylamine followed by oxidation with *m*-CPBA. The isotopic composition of the product mixture was analyzed by FABMS as shown in Table 3. Comparison of the observed isotopic ratio with the expected isotopic distribution for an intramolecular and intermolecular reaction establishes that the transfer of phosphorus in the conversion of **21** to **43** occurs in an intramolecular fashion.

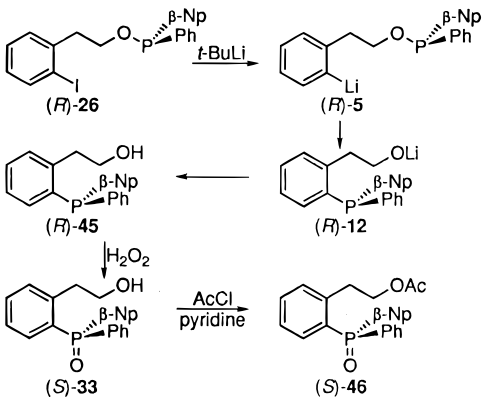
Table 3. Isotopic Ratios for Phosphine Oxide Mixture **41** from the Double Label Experiment using Phosphinite Borane Mixture **21**[a]

	M	*M* + 1	*M* + 2	*M* + 5	*M* + 6	*M* + 7
reactant **21**[b]	55	0	0	0	10	34
product **41**[c]	52	0	1	1	8	35
intramolecular[d]	55	0	0	0	10	34
intermolecular[d]	33	6	19	24	5	14

[a] Determined by FABMS (error ±5%). [b] A mixture of **21** and **21**-d_7 with minor amounts of **21**-d_6. Only one phenyl ring was labeled. [c] Phosphine borane **43** was converted to phosphine oxide **41**. [d] Calculated based on isotopic ratio of **21** and **21**-d_7.



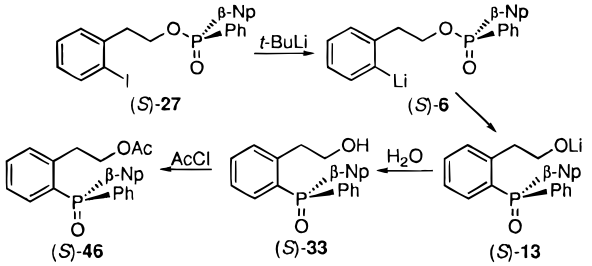
Transfers of Stereogenic Phosphorus: Reaction of Phosphinite (*R*)-26, Phosphinate (*S*)-27, and Phosphinite Borane (*R*)-25 with *t*-BuLi. In order to determine the stereochemical course of the endocyclic nucleophilic substitutions at phosphorus the transfers of phosphorus from oxygen to carbon were examined for the conversions of (*R*)-**5**, (*S*)-**6**, (*R*)-**7**−(*R*)-**12**, (*S*)-**13**, and (*R*)-**14**, respectively. A 0.1 M solution of phosphinite (*R*)-**26** in THF was treated with 2 equiv of *tert*-butyllithium at −78 °C to afford organolithium (*R*)-**5**. Rearrangement of (*R*)-**5** afforded alkoxy phosphine (*R*)-**12**. After 1 min the solution was treated with water to afford phosphine (*R*)-**45** which was oxidized with 30% hydrogen peroxide. The oxidation proceeds with retention of configuration to give phosphine oxide (*S*)-**33**.[18,19] The enantiomeric ratio of (*S*)-**33** was determined to be 94:6 (±5%) by analysis of its acetate derivative (*S*)-**46** by chiral stationary phase (CSP) HPLC while the er for (*R*)-**26** was determined to be 89:11 (±5%).



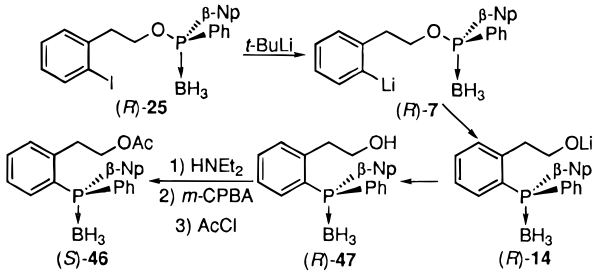
The configuration of (*S*)-**33** was determined by comparing the product to independently synthesized (*S*)-**33** by CSP HPLC

and CD spectroscopy. The *S* configuration at phosphorus in the transfer of phosphorus establishes the conversion of (*R*)-**5** to (*R*)-**12** proceeds with an overall retention of stereochemistry.

The stereochemistry for the transfer of a stereogenic phosphorus(V) atom in the conversion of (*S*)-**6** to phosphine oxide **13** was investigated with phosphinate (*S*)-**27**. Phosphinate (*S*)-**27** with an er of 94:6 was treated with 2 equiv of *tert*-butyllithium in THF at −78 °C to provide lithio phosphine oxide (*S*)-**6**. Rearrangement of (*S*)-**6** afforded alkoxy phosphine oxide (*S*)-**13**. After 1 min the reaction was treated with water, and phosphine oxide (*S*)-**33** was isolated. The enantiomeric ratio of (*S*)-**33** was determined to be 96:4 by analysis of its acetate derivative (*S*)-**46** by CSP HPLC. This result establishes that the transfer of chiral phosphorus(V) in the conversion of (*S*)-**6** to (*S*)-**13** occurs with an overall retention of stereochemistry at phosphorus.



The transfer of a stereogenic phosphorus atom complexed to borane was examined for the conversion of lithio phosphinite borane (*R*)-**7** to alkoxy phosphine borane **14** using phosphinite borane (*R*)-**25**. Phosphinite borane (*R*)-**25** with an er of 94:6 was treated with 2 equiv of *tert*-butyllithium lithio phosphinite borane (*R*)-**7** which led to the alkoxy phosphine borane (*R*)-**14**. After 1 min water was added, and phosphine borane (*R*)-**47** was isolated. The enantiomeric ratio of (*R*)-**47** was determined to be 92:8 by analysis of the acetate derivative (*S*)-**46** prepared by decomplexation of borane, oxidation, and acylation of (*R*)-**47**. The transfer of phosphorus in the conversion of (*R*)-**7** to (*R*)-**14** occurs with an overall retention of stereochemistry at phosphorus.



Discussion

The intramolecular conversions of phosphinite **1** to phosphine **8**, phosphinite **2** to phosphine **9**, phosphinate **3** to phosphine oxide **10**, and phosphinite borane **4** to phosphine borane **11** establish that transfer of phosphorus can occur within either a five- or six-membered endocyclic ring. These results which establish that a 180° angle between the nucleophilic, phosphorus atom, and leaving group is not required for nucleophilic substitution at phosphorus rule out the in-line S_N2 and in-line addition−elimination mechanism for these transfers.[20] The reaction pathways which are consistent with an oblique angle for phosphorus transfer involve addition−elimination sequences.

Four possible addition−elimination pathways are illustrated for the reaction of (*R*)-**5**. (1) Addition of the aryl nucleophile may occur such that the nucleophile is located in an apical position, while the leaving group is in an equatorial position. This intermediate is shown by the trigonal bipyramidal anion **48**.[21] Direct elimination of the equatorial alkoxy leaving group from intermediate **48** would give a product with a retention of stereochemistry. (2) Addition of the aryl nucleophile could occur at an equatorial position with the leaving group axial, shown as phosphorane **49**. Direct loss of the apical alkoxy group from **49** would also afford a product with retention of stereochemistry. (3) An alternative addition of the nucleophile at an equatorial position could occur with the leaving group in a equatorial position, illustrated by intermediate **50**.[22] Direct loss of the equatorial alkoxy group from **50** would lead to an inversion of stereochemistry. (4) A final possibility involves Berry pseudorotation between phosphoranes **48** and **49**.[23] This allows for reorganization around phosphorus in such a manner that two equatorial ligands are exchanged with two apical ligands, while one equatorial ligand remains equatorial as a pivot ligand. This pathway allows either an apical addition-pseudorotation−apical elimination pathway or equatorial addition−pseudorotation−equatorial elimination pathway in addition to more complex pseudorotation pathways. In the endocyclic case apical addition would afford phosphorane **48** followed by pseudorotation to afford phosphorane **49** in which the alkoxy leaving group could depart from the apical position to give retention of configuration. Pathways 1, 2, and 4 all afford the product with a retention of configuration, while pathway 3 yields inversion.

The present work established that the stereochemistry of the endocyclic transfers of phosphorus proceeds with retention of configuration for the conversions of phosphinite (*R*)-**5** to phosphine (*R*)-**12**, phosphinate (*S*)-**6** to phosphine oxide (*S*)-**13**, and phosphinite borane (*R*)-**7** to phosphine borane (*R*)-**14**. On this basis pathway 3 can be ruled out.

Equatorial addition followed by apical elimination or apical addition followed by equatorial elimiation has been suggested and cannot be excluded on the present experimental data.[24,25] However, Mislow suggests that if the bond making or breaking step is rate determining, then apical addition and elimination will be more favorable than equatorial addition and elimination.[25] Based on the assumption that the bond making and breaking process is rate determining, the general interpretation for nucleophilic substitutions which involve trigonal bipyramidal intermediates is that addition of the nucleophile occurs at the apical position and elimination of the leaving group occurs from the apical position.[25,26] When those restrictions are applied to the present cases pathways 1 and 2 can be eliminated. Mechanisms which require pseudorotation to occur following pathway 4 require futher consideration.

(18) Horner, L. *Pure Appl. Chem.* **1964**, *5*, 225.
(19) Other oxidants (*m*-CPBA and *t*-BuOOH) also provide retention of sterochemistry and gave similar results.
(20) The endocyclic restriction test was attempted for a 15- and 18-membered endocyclic ring; however, only intermolecular *t*-butyl addition at phosphorus was observed.
(21) Only one apical addition is shown, but an equivalent apical addition could occur to afford the naphthyl group and nucleophile in apical positions.
(22) An intermediate similar to **41** has been observed by NMR: Ross. M. R.; Martin, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 1234.
(23) Berry, R. S. *J. Chem. Phys.* **1960**, *32*, 933.
(24) () (a) Corriu, R. J. P.; Guerin, C. In *Advances in Organometallic Chemistry*; Stone, F. G. A., West, R., Eds.; Academic Press: New York, 1982; p 265. (b) Corriu, R. J. P.; Guerin, C. *J. Organomet. Chem.* **1980**, *198*, 231.
(25) Mislow, K. *Acc. Chem. Res.* **1970**, *3*, 321.
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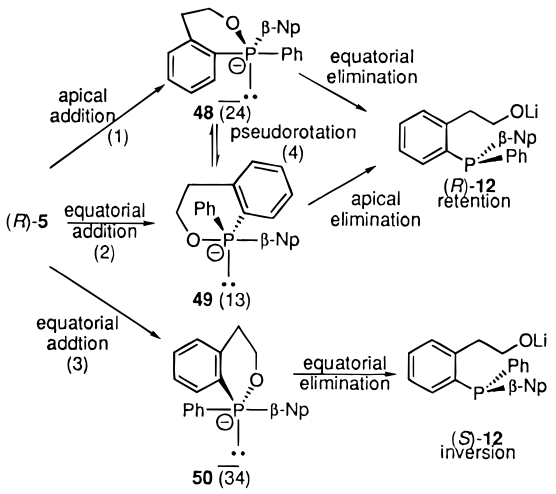


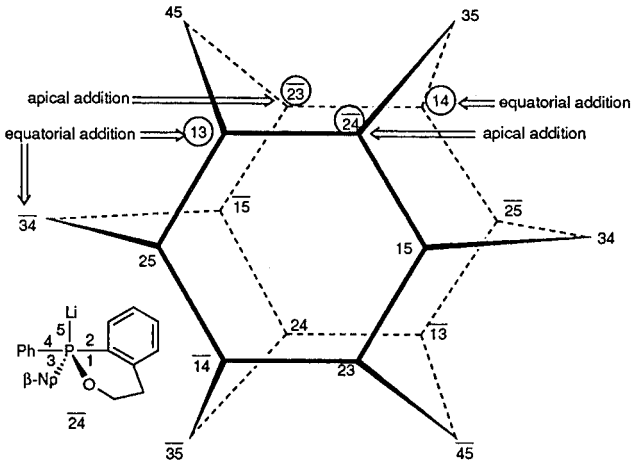


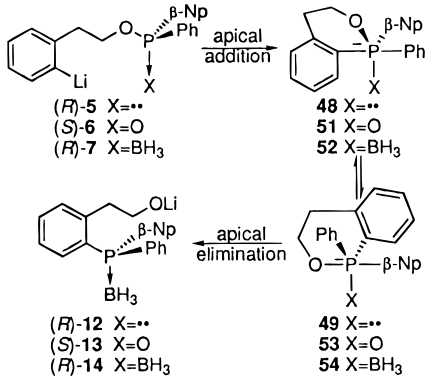
Figure 1. Desargues−Levi diagram.

A Desargues−Levi diagram[25] (Figure 1) illustrates all of the possible pseudorotations for the intermediates in the reaction of (*R*)-**5**. In this diagram each ligand is assigned a number: 1 = alkoxy leaving group, 2 = aryl nucleophile, 3 = b-naphthyl, 4 = phenyl, and 5 = lone pair. The two apical substituents in the trigonal bipyramid are denoted in ascending numerical order for the symbols used at each vertex on the diagram. If the equatorial substituents increase in assigned value in a counterclockwise direction when the trigonal bipyramid is viewed down the apical bonds with the lowest priority apical ligand in back, a bar is placed above the symbol i.e. $\bar{2}\bar{4}$. This nomenclature is illustrated in Figure 1 for phosphorane $\bar{2}\bar{4}$. If the equatorial substituents increase in assigned value in a clockwise direction then no bar is used i.e. 24. Intermediates 12 and O$\bar{1}\bar{2}$ are not shown due to the 180° requirement for the apical−apical placement of the nucleophile and leaving group for intermediate 12 and $\bar{1}\bar{2}$ is not energetically preferred. Each intermediate trigonal bipyramidal anion has two or three possible pseudorotation pathways available to it as indicated by the lines connecting vertices in the diagram. Also indicated on the diagram is the overall stereochemistry of the product resulting from loss of the alkoxide from the TBP intermediate. The intermediates from the top half would result in a retention of configuration while the bottom half leads to inversion.

If the lone pair of electrons is assumed to always occupy an equatorial position a single pathway can be specified for these reactions. The assumption that no pseudorotation can lead to an intermediate containing a lone pair of electrons at the apical position is supported by VSEPR theory,[27] MO calculations[28] and the qualitative considerations of s character.[29] In this case any vertex with a 5 (lone pair) is considered not to be accessible. The only allowed pseudorotations on this energy profile are between intermediates $\bar{2}\bar{4}$ (**48**) and 13(**49**) and between intermediates $\bar{2}\bar{3}$ and 14. All other pseudorotations from these phosphorane intermediates would require placing the lone pair of electrons at the energetically unfavorable apical position.

Indeed, if the lone pair could be apical, then racemization would be expected, for example, $\bar{2}\bar{4}$ (**48**) to 15 would afford inversion. However, in all of the endocyclic cases only retention of configuration with no racemization is observed. Pathway 3 has been eliminated based on the observed retention. In addition the possible pseudorotations from equatorial addition intermediate **50** $\bar{3}\bar{4}$ should not be on the reaction pathway because any pseudorotation from intermediate **50** $\bar{3}\bar{4}$ would involve the energetically unfavorable placement of the lone pair of electrons in an apical position.

Under the above assumptions the only possible addition−pseudorotation−elimination pathway which is consistent with the data is (*R*)-**5** to **48** $\bar{2}\bar{4}$ to **49** (13) to (*R*)-**12**. Apical addition of the aryl group to phosphorus gives the trigonal bipyramidal intermediate **48** $\bar{2}\bar{4}$. Pseudorotation of **48** $\bar{2}\bar{4}$ to **49** (13) reorganizes the bonds about phosphorus such that the leaving group can become apical while maintaining the lone pair in an equatorial position. Loss of the alkoxy leaving group from **49** (13) leads to (*R*)-**12** with a retention of stereochemistry at phosphorus. This process can be generalized for transfer of phosphorus(V) and borane complexed to phosphorus for the endocyclic phosphorus systems investigated in this work. In the cases of intermediates **3**, **4**, **6**, and **7** the oxygen or borane anion is required to always remain in the equatorial position.



The calculations of Bachrach and Mulhearn[27] for the reaction of hydride with phosphine are consistent with the assigned mechanism. The addition of hydride at phosphine is calculated to occur at an apical position to form a C_{2v} phosphorane anion as a discrete intermediate. Pseudorotation is calculated to occur through a C_{4v} transition state with the lone pair of electrons always in an equatorial position. Placement of the lone pair of electrons at an apical position was calculated to be 30.33 kcal/mol higher in energy than the C_{2v} phosphorane with the lone pair equatorial. Attempts to find the C_1 transition state structure leading to an apical lone pair of electrons were unsuccessful in the calculations.

Precedent for the proposed pathways exists.[7,26] Retention of configuration at phosphorus has been observed in the hydrolysis

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of constrained phosphate triesters and of phophetanes.[7] In each of those cases the leaving group and nucleophile were unable to both occupy apical position simultaneously.

The present endocyclic reactions which proceed with retention at phosphorus are different from the acyclic cases where inversion of stereochemistry is observed.[1,4] This difference illustrates the fact that this endocyclic restriction test is permissive in the sense that an endocyclic reaction may proceed via a different pathway than an unconstrained reaction. The endocyclic test indicates what nucleophilic trajectories are possible and cannot by itself rule out geometries not tested. The in-line S_N2 pathway and in-line addition−elimination pathway is unavailable in the endocyclic systems due to the restriction of the tether. It is possible that the endocyclic system is related to the acyclic system and both proceed through a TBP intermediate in an addition−elimination mechanism. In the acyclic reaction apical addition of the nucleophile can occur opposite the leaving group allowing direct apical loss of the leaving group leading to an inversion of configuration. However, in the endocyclic cases the leaving group is not properly situated in an apical position after apical attack of the nucleophile therefore pseudorotation must occur after apical addition in order to allow apical elimination of the alkoxy group.

Conclusion

The transfer of phosphorus in the conversions of lithio phosphinite **1** to alkoxy phosphine **8**, of lithio phosphinite **2** to alkoxy phosphine **9**, of lithio phosphinate **3** to alkoxy phosphine oxide **10**, and of lithio phosphinite borane **4** to alkoxy phosphine borane **11** can occur in an intramolecular endocyclic fashion. These results ruled out the in-line S_N2 and in-line addition−elimination mechanisms in these cases. The observed retention of stereochemistry at phosphorus for the transfer of stereogenic phosphorus in the conversions of lithio phosphinite **5** to alkoxy phosphine **12**, of lithio phosphinate **6** to alkoxy phosphine oxide **13**, and of lithio phosphinite borane **7** to alkoxy phosphine borane **14** differs from the observed inversion of configuration in acyclic reactions. The endocyclic transfers of phosphorus are proposed to follow an addition−pseudorotation−elimination pathways shown for **48** to **49**, **51** to **53**, and **52** to **54**. In these reactions apical addition of the nucleophile is followed by pseudorotation of the trigonal bipyramidal intermediate and apical loss of the leaving group to give retention of stereochemistry at phosphorus.

Experimental Section

General Methods. All reagents were obtained from commercial sources and used without further purification unless stated otherwise. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried and distilled over sodium and acetophenone. Hexanes were distilled prior to use. See supporting information.

2-(*o*-Iodophenethyl) Diphenylphosphinite (18). To a solution of 420 mg (1.73 mmol) of *o*-iodophenethyl alcohol in 11.2 mL of THF cooled to −20 °C in an ice salt bath were added 1.14 mL (6.54 mmol) of diisopropylethylamine and 415 mL of chlorodiphenylphosphine. The solution was stirred 30 min at −20 °C. The amine hydrochloride was removed via vacuum filtration, and the THF was removed in vacuo. The resulting mixture was chromatographed on a neutral alumina (20% EtOAc in hexane) to yield 614 mg (82%) of 2-(*o*-iodophenethyl) diphenylphosphinite as a colorless oil. ^{1}H NMR (400 MHz) δ 3.12 (t, J = 7.08 Hz, 2H), 4.00−4.12 (m, 2H), 6.86−6.91 (m, 1H), 7.31−7.46 (m, 12 H), 7.79 (d, J = 7.81 Hz). ^{13}C NMR (100 MHz) δ 42.44 (d, J = 7.6 Hz), 68.83 (d, J = 19.1 Hz), 100.73, 128.13, 128.18, 128.25, 129.21, 130.32 (d, J = 22.1 Hz), 130.47, 139.38, 140.73, 141.66 (d, J = 18.3 Hz). ^{31}P NMR (162 MHz) δ 113.42. FIMS *m/z* 305 (M − I). Anal. Calcd for $C_{20}H_{18}IOP$: C, 55.58; H, 4.20. Found: C, 55.82; H, 4.23.

2-*o*-Iodophenethyl Alcohol-(α,α)-*d*$_2$ (16-*d*$_2$). A solution of 2.0 g (7.63 mmol) of *o*-iodophenylacetic acid in 5.9 mL THF was cooled in an ice bath to 0 °C. To the solution was added 550 mg (13.14 mmol) of sodium borodeuteride. A solution of 1.2 mL (9.60 mmol) of boron trifluoride etherate in 2.3 mL of THF was added dropwise to the *o*-iodophenylacetic acid solution at 0 °C. The solution was warmed to room temperature and stirred overnight. The reaction mixture was quenched with saturated sodium carbonate solution. The resulting mixture was extracted twice with benzene. The combined organics were washed with 5% NaOH solution and saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed in vacuo and further purification by vacuum distillation at 156 °C/5 Torr yielded 1.41 g (74%) of 2-*o*-iodophenethyl alcohol-*d*$_2$ (**16**-*d*$_2$). ^{1}H NMR (300 MHz) δ 1.92 (br s, 1H, OH), 2.98 (s, 2H), 6.86−6.92 (m, 1H), 7.24−7.35 (m, 2H), 7.81 (d, J = 7.82 Hz, 1H). ^{13}C NMR (75 MHz) δ 43.40, 61.64 (m), 100.74, 128.23, 128.26, 130.26, 139.53, 140.98. EIMS *m/z* 250.

(*o*-Iodophenethyl-*d*$_2$) Di(phenyl-*d*$_5$)phosphinite (18-*d*$_{12}$). To a solution of 500 mg (2.0 mmol) of *o*-iodophenethyl alcohol-*d*$_2$ (**16**-*d*$_2$) in 13 mL of THF cooled to −20 °C in a ice salt bath was added 1.33 mL of diisopropylethylamine and 380 mL of diphenylphosphinous chloride-*d*$_{10}$ (**17**-*d*$_{10}$). The solution was stirred 30 min at −20 °C. The amine hydrochloride was removed by vacuum filtration, and the THF was removed in vacuo. The resulting mixture was chromatographed on neutral alumina (20% EtOAc in hexane) to yield 526 mg (59%) of **18**-*d*$_{12}$ as a colorless oil. ^{1}H NMR (400 MHz) δ 3.10 (s, 2H), 6.83−6.88 (m, 1H), 7.18−7.19 (m, 2H), 7.77 (d, J = 7.81 Hz). ^{13}C NMR (100 MHz) δ 42.28 (d, J = 8.6 Hz), 68.35 (m), 100.73, 127.65 (t, J = 24.4 Hz)), 127.72 (t, J = 24.0 Hz), 128.12, 128.17, 128.92 (t, J = 24.0 Hz), 129.77 (t, J = 23.7 Hz), 130.00 (t J = 23.3 Hz), 130.36, 130.44, 140.71, 141.44 (d, J = 17.6 Hz). ^{31}P NMR (162 MHz) δ 113.21. FIMS *m/z* 317 (M − I). *d*$_{12}$, 84%; *d*$_{11}$, 12%.

***O*-(*o*-Iodobenzyl) Diphenylphosphinate (20).** To a solution of 200 mg (0.48 mmol) **18** in 20 mL ethyl acetate was added 150 mg (0.74 mmol) *m*-CPBA and the solution was stirred 30 min then washed with saturated aqueous Na_2CO_3 and brine. The solution was dried over sodium sulfate, and filtered, and the solvent evaporated in vacuo. The residue was purified by MPLC (30% EtOAc in hexane) to yield 187 mg (90%) of **20** as a white solid. Mp = 62−63 °C. ^{1}H NMR (300 MHz) δ 5.07 (d, J = 6.7 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.37−7.54 (m, 7H), 7.78−7.89 (m, 5H). ^{13}C NMR (125MHz) δ 69.89 (d, J = 5.0 Hz), 97.45, 128.29, 128.49 (d, J = 12.5 Hz), 129.05, 129.71, 130.50, 131.60 (d, J = 10 Hz), 132.22, 138.65 (d, J = 7.5 Hz), 139.21. ^{31}P NMR (121 MHz) δ 33.16. FABMS *m/z* 435 $(M + H)^+$. Anal. Calcd for $C_{19}H_{16}IO_2P$: C, 52.56; H, 3.71. Found: C, 52.75; H, 3.74.

***O*-(*o*-Iodobenzyl-*d*$_2$) Di(phenyl-*d*$_5$)phosphinate (20-*d*$_{12}$).** Labeled phosphinite **20**-*d*$_{12}$ was prepared in a manner analogous to **20** above in 80% yield. ^{31}P NMR (121 MHz) δ 33.16.

***O*-*o*-Iodobenzyl Diphenylphosphinite Borane (21).** To a solution of 2.0 g (8.54 mmol) of *o*-iodobenzyl alcohol, 5.0 mL of (28.70 mmol) diisopropylethylamine and 50 mL of THF cooled to 0 °C was added 1.8 mL (10.02 mmol) of diphenylphosphinous chloride, and the solution was stirred 30 min at 0 °C. The amine hydrochloride salt was filtered, and the THF was removed in vacuo. The resulting oil was dissolved in 50 mL of toluene, and 2.0 mL (20.0 mmol) of 10 M borane-dimethyl sulfide complex was added. The solution was stirred 3 days, and the solvent was removed in vacuo. The resulting oil was purified by chromatography on silica (10% EtOAc in hexane) to yield a white solid. Recrystallization of the solid (methanol) yielded 1.49 g (40%) of *O*-*o*-iodobenzyl diphenylphosphinite borane (**21**). Mp 79−80 °C. ^{31}P NMR (162 MHz) δ 107.5 (q, J = 76 Hz). ^{1}H NMR (400 MHz) δ 0.6−1.6 (m, 3H), 4.89 (d, J = 6.6 Hz, 2H), 6.81−6.85 (m, 1H), 7.14−7.18 (m, 1H), 7.27−7.37 (m, 7H), 7.63−7.68 (m, 5H). ^{13}C NMR (100 MHz) δ 72.30, 97.60, 128.17, 128.47 (d, J = 10.7 Hz), 129.08, 131.08 (d, J = 11.4 Hz), 131.64, 131.82 (d, J = 2.3 Hz), 138.68 (d, J = 8.4 Hz), 139.08. FABMS *m/z* 103(29), 119(59), 121(13), 135(35), 149(12), 152-(30), 153(17), 154(11), 155(38), 201(31), 203(15), 217(39), 291(32), 303(13), 419(29), 430(11), 431(39). Anal. Calcd for $C_{19}H_{19}BIOP$: C, 52.82; H, 4.43. Found: C, 53.20; H, 4.56.

***O*-*o*-Iodobenzyl Diphenylphosphinite Borane-*d*$_7$ (21-*d*$_7$)**. To a solution of 375 mg (1.59 mmol) of *o*-iodobenzyl alcohol-*d*$_2$, 825 μL

(4.77 mmol) of diisopropylethyl amine, and 10.6 mL of THF cooled to 0 °C was added 360 mg (1.60 mmol) of diphenylphosphinous chloride-d_5 (**17**-d_5). The solution was stirred 1 h at 0 °C. The precipitate was filtered, and the solvent was removed in vacuo. The oil was dissolved in 11 mL of toluene, and 300 μL of BH_3·SMe_2 was added. The solution was stirred 3 days, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica (10% EtOAc in hexane) followed by HPLC (10% EtOAc in hexane) to yield 138 mg (20%) **21**-d_7. ^{31}P NMR (162 MHz) δ 107.55 (q, J = 79 Hz). ^{1}H NMR (400 MHz) δ 0.7−1.7 (m, 3H), 6.99−7.084 (m, 9H). Isotopic analysis (EIMS) 50% d_7, 41% d_6, 8% d_5, 1% d_4.

***(R)*-*O*-(2-(*o*-Iodophenyl)ethyl) (2-Naphthyl)phenylphosphinite Borane ((*R*)-25).** To a solution of 5.19 g (12.56 mmol) of aminophosphine borane (*S*)-**24** in 5 mL of THF was added 13.59 mL (54.78 mmol) of *o*-iodophenethyl alcohol and 700 μL (12.60 mmol) 18 M sulfuric acid. The resulting reaction mixture was stirred 16 h. Ether was added to the reaction mixture, and it was washed with 10% aqueous H_2SO_4 solution. The extracts were dried over sodium sulfate, filtered, and solvent evaporated in vacuo. The resulting residue was purified by flash chromatography on silica (10% EtOAc in hexane) to yield 1.51 g (24%) of (*R*)-**25** as a colorless oil. ^{31}P NMR (162 MHz) δ 105.6 (m). ^{1}H NMR (400 MHz) δ 0.6−1.6 (m, 3H), 3.06 (t, J = 6.8 Hz, 2H), 4.08−4.14 (m, 2H), 6.77−6.82 (m, 1H), 7.11−7.14 (m, 2H), 7.27−7.49 (m, 6H), 7.56−7.61 (m, 2H), 7.70−7.77 (m, 4H), 8.19 (d, J = 12.7 Hz, 1H). ^{13}C NMR (100 MHz) δ 41.65 (d, J = 6.8 Hz), 66.23 (d, J = 2.3 Hz), 125.80 (d, J = 9.9 Hz), 126.81, 127.70, 128.12, 128.22, 128.37, 128.47, 128.49, 128.60,129.11, 130.57, 131.11 (d, J = 11.5 Hz), 131.76 (d, J = 2.3 Hz), 131.80 (d, J = 64.1 Hz), 132.33 (d, J = 12.2 Hz), 134.54 (d, J = 1.5 Hz), 139.45, 139.98. Anal. Calcd for $C_{24}H_{23}BIOP$: C, 58.10; H, 4.67. Found: C, 58.27; H, 4.86. $[\alpha]_D$ = +12.5±0.2° (*c* 2.51, $CDCl_3$).

***(R)*-*O*-(2-(*o*-Iodophenyl)ethyl) (2-Naphthyl)phenylphosphinite ((*R*)-26).** A solution of 1.51 g (3.04 mmol) of phosphinite borane (*R*)-**25** in 25 mL of diethylamine was heated at reflux for 2 h. The amine was removed in vacuo and purified by flash chromatography on neutral alumina (10% EtOAc in hexane) to yield 1.47 g (100%) of phosphinite (*R*)-**26** as a colorless oil. ^{31}P NMR (162 MHz) δ 113.89 (m). ^{1}H NMR (400 MHz) δ 3.39 (t, J = 7.0 Hz, 2H), 4.33 (dt, J = 9.0, 7.0 Hz, 2H), 7.07−7.13 (m, 1H), 7.40−7.78 (m, 9H), 7.98−8.17 (m, 5H), 8.27 (d, J = 8.8 Hz). ^{13}C NMR (400 MHz) δ 42.49 (d, J = 7.8 Hz), 68.91 (d, J = 18.3 Hz), 125.75, 126.21, 126.29, 126.37, 126.59, 126.70, 127.62, 127.70, 127.81, 127.91 (d, J = 6.0 Hz), 128.13, 128.20, 128.26, 128.29, 129.23, 130.27, 130.53 (d, J = 3.4 Hz), 131.20 (d, J = 28.3 Hz), 133.74, 139.43. $[\alpha]_D$ = +23.5 ± 0.7° (*c* 0.56, $CDCl_3$).

***(S)*-*O*-(2-(*o*-Iodophenyl)ethyl) (2-Naphthyl)phenylphosphinate ((*S*)-27).** To a solution of 207 mg (0.43 mmol) of phosphinite (*R*)-**26** in 4 mL of THF was added 135 mg of 55% *m*-CPBA and was stirred for 1 h. Ether was added to the solution and was washed with 5% aqueous NaOH solution, 5% aqueous HCl solution, and brine. The extracts were dried over magnesium sulfate, filtered, and solvent evaporated in vacuo. The residue was purified by MPLC (50% EtOAc in hexane) to yield 142 mg (66%) of phosphinate (*S*)-**27** as a colorless oil. ^{31}P NMR (162 MHz) δ 32.73. ^{1}H NMR (400 MHz) δ 3.21 (t, J = 6.8 Hz, 2H), 4.24−4.30 (m, 2H), 6.91−6.95 (m, 1H), 7.26−7.29 (m, 2H), 7.39−7.43 (m, 2H), 7.47−7.65 (m, 4H), 7.73−7.90 (m, 6H), 8.38 (d, J = 14.2 Hz, 1H). ^{13}C NMR (100 MHz) δ 41.47 (d, J = 7.7 Hz), 63.81 (d, J = 6.1 Hz), 100.58, 126.21 (d, J = 11.4 Hz), 126.79, 127.36, 127.70, 128.19, 128.24, 128.29, 128.42, 128.55, 128.91, 130.66, 131.15 (d, J = 138 Hz), 131.50, 131.60, 132.12 (d, J = 3.1 Hz), 132.30 (d, J = 14.5 Hz), 134.73 (d, J = 2.3 Hz), 139.51, 139.96. Anal. Calcd for $C_{24}H_{20}IO_2P$: C, 57.85; H, 4.04. Found: C, 57.94; H, 4.43.

***(S)*-(*N*-((*1R,2S*)-2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl)-amino((*o*-methoxyethyl)phenyl)phenylphosphine Borane ((*S*)-29).** To a solution of 1.95 g (9.07 mmol) of *o*-bromo(methoxyethyl)benzene in 10 mL of ether cooled to −78 °C was added 13.95 mL (18.14 mmol) of 1.3 M *tert*-butyllithium, and the solution was stirred 5 min at −78 °C. The resulting organolithium solution was added dropwise to a solution of 2.60 g (9.12 mmol) of oxazaphospholidine borane (*R*)-**23** in 5 mL of THF and 15 mL of ether cooled to −78 °C, stirred 0.5 h at −78 °C, warmed to room temperature, and stirred 1 h. The reaction mixture was quenched with water, ether extracted, dried over sodium sulfate, and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica (10−30% EtOAc in hexane) to yield 2.16 g (57%) of (*S*)-**29** as a white solid. Mp = 97−98 °C. ^{31}P NMR (162 MHz) δ 70.89 (m). ^{1}H NMR (400 MHz) δ 0.5−1.6 (m, 3H), 1.24 (d, J = 7.1 Hz, 3H), 1.84 (br s, 1H), 2.63 (d, J = 7.6 Hz, 3H), 2.91−3.02 (m, 2H), 3.27 (s, 3H), 3.54−3.58 (m, 2H), 4.29−4.34 (m, 1H), 4.95 (d, J = 3.7 Hz, 1H), 7.21−7.32 (m, 5H), 7.38−7.49 (m, 7H), 7.55−7.60 (m, 2H). ^{13}C NMR (100 MHz) δ 11.45 (d, J = 4.6 Hz), 31.59 (d, J = 3.0 Hz), 33.83 (d, J = 4.6 Hz), 58.04 (d, J = 9.9 Hz), 58.48, 72.99, 79.02 (d, J = 1.6 Hz), 125.95, 126.07 (d, J = 9.2 Hz), 127.41, 128.28, 128.46 (d, J = 9.9 Hz), 128.68, 130.80 (d, J = 2.3 Hz), 130.97 (d, J = 1.5 Hz), 131.29 (d, J = 9.2 Hz), 131.78 (d, J = 9.9 Hz), 132.25, 132.86, 132.94 (d, J = 8.3 Hz), 142.53. Anal. Calcd for $C_{25}H_{33}BNO_2P$: C, 71.27; H, 7.89; N, 3.32. Found: C, 71.03; H, 7.96; N, 3.44.

***(R)*-*O*-Methyl (*o*-(methoxyethyl)phenyl)phenylphosphine Borane ((*R*)-30).** To a solution of 2.16 g (5.13 mmol) of aminophosphine borane (*S*)-**29** in 50 mL of methanol was added 285 μL of 18 M sulfuric acid, and the resulting mixture was stirred overnight. To the solution was added saturated aqueous sodium carbonate solution, and the methanol was removed in vacuo. The solution was ether extracted, dried over sodium sulfate, and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica (10% EtOAc in hexane) to yield 950 mg (64%) of (*R*)-**30** as a colorless oil. ^{31}P NMR (162 MHz) δ 110.0 (m). ^{1}H NMR (400 MHz) δ 0.6−1.6 (m, 3H), 2.82 (t, J = 7.3 Hz, 2H), 3.06 (s, 3H), 3.11 (dt, J = 7.3, 1.7 Hz, 2H), 3.63 (d, J = 12.2 Hz, 3H), 7.20−7.24 (m,2H), 7.52−7.57 (m, 4H), 7.75−7.80 (m, 1H). ^{13}C NMR (100 MHz) δ 33.76 (d, J = 4.6 Hz), 53.89 (d, J = 2.3 Hz), 58.31, 72.51, 126.18 (d, J = 11.4 Hz), 128.57 (d, J = 10.6 Hz), 129.38 (d, J = 59.5 Hz), 131.04 (d, J = 10.6 Hz), 131.21 (d, J = 8.4 Hz), 131.69 (d, J = 2.3 Hz), 132.15 (d, J = 2.2 Hz), 132.23 (d, J = 64.1 Hz), 133.57 (d, J = 15.2 Hz), 142.43 (d, J = 8.4 Hz). Anal. Calcd for $C_{16}H_{22}BO_2P$: C, 66.70; H, 7.69, H. Found: C, 66.31; H, 7.85.

***(R)*-((*o*-Methoxyethyl)phenyl)(*β*-naphthyl)phenylphosphine Borane ((*R*)-31).** To a solution of 1.35 g (6.52 mmol) of *β*-bromonaphthalene in 16 mL of THF cooled to −78 °C was added 9.3 mL (13.02 mmol) of 1.4 M *tert*-butyllithium, and the solution was stirred 5 min at −78 °C. The resulting naphthyllithium solution was added to a solution of 940 mg (3.26 mmol) of phosphinite borane (*R*)-**30** in 16 mL of THF at −78 °C. The reaction mixture was stirred for 1 h while warming to 0 °C and an additional hour at room temperature. The reaction was quenched with water, and the THF was removed in vacuo. The residue was dissolved in ether, washed with saturated aqueous NaCl solution, dried over sodium sulfate, and filtered, and solvent removed in vacuo. The residue was purified by flash chromatography on silica (5% EtOAc in hexane) and recrystallized with dichloromethane and hexane to yield 354 mg (28%) of phosphine borane (*R*)-**31** as a colorless oil. ^{31}P NMR (162 MHz) δ 21.1 (m). ^{1}H NMR (400 MHz) δ 0.7−1.8 (m, 3H), 2.89 (dt, J = 2.5, 6.7 Hz, 2H), 3.05 (s, 3H), 3.28 (dt, J = 3.4, 7.1 Hz, 2H), 6.98−7.01 (m, 1H), 7.09−7.11 (m, 1H), 7.37−7.60 (m, 10H), 7.76−7.83 (m, 3H), 8.10 (d, J = 13.0 Hz, 1H). ^{13}C NMR (100 MHz) δ 34.62 (d, J = 6.1 Hz), 58.30, 72.55, 126.23 (d, J = 58.0 Hz), 126.38 (d, J = 9.1 Hz), 126.88, 127.55, 127.76, 128.08, 128.16 (d, J = 4.6 Hz), 128.55 (d, J = 9.2 Hz), 128.76, 128.83, 128.94, 129.40 (d, J = 58.0 Hz), 131.27 (d, J = 2.2 Hz), 131.38, 131.47, 132.75 (d, J = 9.4 Hz), 133.25 (d, J = 9.2 Hz), 134.25 (d, J = 1.5 Hz), 134.55 (d, J = 8.4 Hz), 143.87 (d, J = 10.7 Hz). $[\alpha]_D$ = +81.7±0.7° (*c* 0.63, $CDCl_3$). Anal. Calcd for $C_{25}H_{26}BOP$: C, 78.15; H, 6.82. Found: C, 78.15; H, 6.76.

***(S)*-((*o*-Methoxyethyl)phenyl)(*β*-naphthyl)phenylphosphine Oxide ((*S*)-32).** A solution of 24 mg (0.06 mmol) of phosphine borane (*R*)-**31** and 1.0 mL of diethylamine was heated at reflux for 1 h. The diethylamine was removed in vacuo. The residue was dissolved in 1.0 mL of ether, and 20 mg (0.06 mmol) of *m*-CPBA was added. The solution was stirred 0.5 h followed by washing with 10% aqueous NaOH solution. The extracts were dried over sodium sulfate and filtered, and the solvent was removed in vacuo to yield 24 mg (100%) of phosphine oxide (*S*)-**32** as a colorless oil. ^{31}P NMR (162 MHz) δ 32.41. ^{1}H NMR (400 MHz) δ 3.16 (s, 3H), 3.18−3.22 (m, 2H), 3.48 (t, J = 6.4 Hz, 2H), 7.10−7.16 (m, 2H), 7.44−7.60 (m, 8H), 7.67−7.72 (m, 2H), 7.86−7.92 (m, 3H), 8.28 (d, J = 14.0 Hz, 1H). ^{13}C NMR (100 MHz) δ 34.42 (d, J = 4.6 Hz), 58.23, 72.68, 125.63 (d, J

= 12.2 Hz), 126.76, 126.87, 127.76, 128.14, 128.27, 128.52 (d, J = 12.2 Hz), 128.90, 130.06 (d, J = 103.8 Hz), 130.95 (d, J = 103.0 Hz), 131.47, 131.81 (d, J = 5.3 Hz), 131.94, 132.01 (d, J = 2.3 Hz), 132.40 (d, J = 13.7 Hz), 133.03 (d, J = 103.8 Hz), 133.04 (d, J = 103.8 Hz), 133.65, 133.65 (d, J = 13.0 Hz), 134.55 (d, J = 2.2 Hz), 144.27 (d, J = 7.0 Hz).

***(S)*-((*o*-Hydroxyethyl)phenyl)(*β*-naphthyl)phenylphosphine Oxide ((*S*)-33).** To a solution of 25.8 mg (0.07 mmol) of (*S*)-**32** in 1 mL of dichloromethane cooled to −78 °C was added 12 μL (0.13 mmol) of boron tribromide. The solution was stirred for 45 min. Saturated aqueous sodium bicarbonate was added, extracted, and washed with brine. The extract was dried over magnesium sulfate and filtered, and the solvent removed in vacuo to yield 1.8 mg (7%) (*S*)-**33** as a colorless oil. ^{31}P NMR (162 MHz) δ 35.91. ^{1}H NMR (400 MHz) δ 3.07−3.10 (m, 2H), 3.92−3.94 (m, 2H), 6.95−7.01 (m, 1H), 7.15−7.20 (m, 1H), 7.44−7.62 (m, 10H), 7.86−7.92 (m, 3H), 8.20 (d, J = 13.4 Hz, 1H). This spetral data is identical to (*S*)-**33** prepared below.

Diphenyl *o*-(Methoxyethyl)phenylphosphine Oxide. To a solution of 1.26 g (5.84 mmol) of 1-bromo-2-methoxyethylbenzene in 1.05 mL of THF cooled to −78 °C was added 8.35 mL (11.69 mmol) of 1.4 M *t*-butyllithium. After 30 min 1.05 mL (5.84 mmol) of diphenylphosphinous chloride was added dropwise, and the solution was stirred 30 min at −78 °C and an additional 30 min at room temperature. To the reaction mixture was added 1.80 g (5.95 mmol) of *m*-CPBA and stirred 30 min at room temperature. Ether was added, the solution was washed with saturated aqueous Na_2CO_3 solution and brine, dried over magnesium sulfate and filtered, and the solvent evaporated. The residue was purified by flash chromatography on silica (50−100% EtOAc in hexane) to yield 923 mg (47%) ether as a colorless oil. ^{31}P NMR (162 MHz) δ 32.19. ^{1}H NMR (400 MHz) δ 1.18 (t, J = 6.9 Hz, 2H), 3.17 (s, 3H), 3.44 (t, J = 6.6 Hz, 2H), 7.00−7.07 (m, 1H), 7.11−7.17 (m, 1H), 7.42−7.66 (m, 11H), 7.88−7.92 (m, 1H).

Diphenyl (*o*-(2-Hydroxyethyl)phenyl)phosphine Oxide (37). To a solution of 923 mg (2.74 mmol) of diphenyl *o*-(methoxyethyl)-phenylphosphine oxide in 3 mL of CH_2Cl_2 at −78 °C was added a solution of 650 μL (6.88 mmol) of BBr_3 in 3 mL of CH_2Cl_2 dropwise, and the solution was stirred 2 h while warming to 0 °C. Water was added, the solution was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over sodium sulfate, and filtered, and the solvent evaporated. Upon standing the colorless oil solidified. Mp = 166−168 °C (lit.[29] 168−169 °C). ^{31}P NMR (162 MHz) δ 35.92. ^{1}H NMR (400 MHz) δ 3.07 (t, J = 5.6 Hz, 2H), 3.91 (t, J = 5.6 Hz, 2H), 4.95 (br s, 1H), 6.91−6.97 (m, 1H), 7.14−7.18 (m, 1H), 7.41−7.62 (m, 12H).

Conversion of Phosphinite 18 to Phosphine 35. To a solution of 231 mg (0.54 mmol) of **18** in 4.05 mL of THF cooled to −78 °C was added 735 μL (0.72 mmol) of 1.02 M *tert*-butyllithium, and the solution was stirred 1 min at −78 °C. The reaction mixture was quenched with saturated aqueous $NaHSO_3$ and ethyl acetate was added. The organic layer was separated and washed with brine, dried over sodium sulfate, and filtered and the solvent evaporated in vacuo. The residue was purified by MPLC (30% EtOAc in hexane) to yield 39 mg (24%) **35** as a colorless oil. ^{31}P NMR (162 MHz) δ −14.80. ^{1}H NMR (400 MHz) δ 1.63 (br s, 1H), 3.14 (t, J = 6.8 Hz, 2H), 3.80 (t, J = 6.8 Hz, 2H), 6.88−6.91 (m, 1H), 7.12−7.16 (m, 1H), 7.23−7.34 (m, 12H). ^{13}C NMR (100 MHz) δ 37.69 (d, J = 19.9 Hz), 63.39 (d, J = 3.1 Hz), 126.82, 128.54 (d, J = 6.9 Hz), 128.74, 129.08, 129.94 (d, J = 5.3 Hz), 133.79 (d, J = 19.8 Hz), 133.92, 135.95 (d, J = 8.2 Hz), 136.48 (d, J = 9.1 Hz), 142.97 (d, J = 25.9 Hz). FIMS *m/z* 306.

Oxidation of phosphine **35** with *m*-CPBA affords phosphine oxide **38** with ^{31}P and ^{1}H NMR identical to above.

An additional experiment where the product mixture was oxidized with *m*-CPBA indicated three phosphorus containing products: (*o*-(2-hydroxyethyl)phenyl)diphenylphosphine oxide (**38**, 43%), phenethyl diphenylphosphinate (**39**, 41%), and *t*-butyldiphenylphosphine oxide (**40**, 16%). **39**: ^{31}P NMR (162 MHz) δ 32.13. ^{1}H NMR (400 MHz) δ 3.04 (t, J = 6.8 Hz, 2H), 4.18−4.24 (m, 2H), 7.19−7.32 (m, 5H), 7.37−7.51 (m, 6H), 7.67−7.72 (m, 4H). **40**: ^{31}P NMR (162 MHz) δ 39.57. ^{1}H NMR (400 MHz) δ 1.23 (d, J = 14.9 Hz, 9H), 7.43−7.52 (m, 7H), 7.92−7.96 (m, 3H).

Endocyclic Restriction Test of 18 and 18-*d*$_{12}$. A solution of 151 mg (0.350 mmol) of 2-(*o*-iodophenethyl) diphenylphosphinite (**18**) and 156 mg (0.350 mmol) of 2-(2-iodophenyl)ethyl) diphenylphosphinite-*d*$_{12}$ (**18**-*d*$_{12}$) in 5.2 mL of THF was cooled to −78 °C. An aliquot was taken for mass spectral analysis. Another solution of 905 mL (0.923 mmol) of *tert*-butyllithium (1.0 M in pentane) was cooled to −78 °C and then added to the phosphinite solution. After 1 min the reaction mixture was quenched with saturated aqueous sodium bisulfite solution. Dichloromethane was added, and the mixture was extracted with brine. The resulting mixture was dried over sodium sulfate and filtered, and the solvent was removed in vacuo to yield a yellow oil. The oil was purified by MPLC (silica gel, 30% EtOAc in hexane) to yield 36 mg (16%) of **35** as a colorless oil. ^{31}P NMR (161 MHz) δ -14.68, −15.13. For isotopic analysis see Table 1.

Preparation of Phosphine Oxide 41. To a solution of 200 mg (0.48 mmol) of **19** in 4 mL of THF cooled to −78 °C was added 1.0 mL (1.0 mmol) of 1 M *tert*-butyllithium and was stirred 10 min at −78 °C. The reaction mixture was quenched with saturated aqueous Na_2CO_3, and ethyl acetate was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered, and the solvent evaporated in vacuo. The residue was purified by MPLC (20% EtOAc in hexane) to give 100 mg (66%) of a colorless oil.

To a stirred solution of 100 mg (0.34 mmol) of the phosphine oil in 10 mL ethyl acetate was added 100 mg (0.54 mmol) of *m*-CPBA, and the solution was stirred 30 min. The solution was washed with saturated aqueous Na_2CO_3 and brine, dried over Na_2SO_4, and filtered, and the solvent evaporated in vacuo. The residue was purified by MPLC (70% EtOAc in hexane) to yield 100 mg (95%) of **41** as a white solid. Mp = 152−153 °C (lit.[30] 158−159 °C). ^{31}P NMR (121 MHz) δ 35.5. ^{1}H NMR (400 MHz) δ 4.58 (s, 2H), 5.50 (br s, 1H), 6.99−7.06 (m, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.46−7.64 (m, 12H). ^{13}C NMR (100 MHz) δ 64.64 (d, J = 5.0 Hz), 127.16 (d, J = 13.8 Hz), 128.65 (d, J = 12.5 Hz), 130.78, 131.22, 131.54 (d, J = 11.3 Hz), 132.00 (d, J = 10.0 Hz), 132.27, 132.75, 133.65 (d, J = 12.5 Hz), 146.58 (d, J = 7.5 Hz). Anal. Calcd for $C_{19}H_{17}O_2P$: C, 74.02; H, 5.56. Found: C, 73.99; H, 5.56.

Endocyclic Restriction Test of 20 and 20-*d*$_{12}$. An approximate 1:1 mixture of 127 mg (0.29 mmol) of **20** and **20**-*d*$_{12}$ was dissolved in 29 mL of THF and an aliquot was removed for FABMS analysis. To the solution cooled to −78 °C was added 610 μL (0.61 mmol) of 1.0 M *tert*-butyllithium, and the solution was stirred 30 min at −78 °C. The reaction mixture was quenched with water and stirred 5 min, and ethyl acetate was added. The organic layer was separated, washed with brine, dried over sodium sulfate and filtered, and the solvent evaporated in vacuo. The residue was purified by MPLC (70% EtOAc in hexane) to yield 43 mg (47%) of **41** as a white solid. Mp = 152−153 °C. ^{31}P NMR (121 MHz) δ 35.44. For isotopic analysis see Table 2.

Conversion of Phosphinite Borane 21 to Phosphine Borane 43. To a solution of 500 mg (1.16 mmol), **21** in 7.7 mL, THF cooled to −78 °C was added 1.8 mL (2.34 mmol) of 1.3 M *tert*-butyllithium, and the solution was stirred 5 min at −78 °C. The reaction mixture was quenched with water, and the THF was evaporated in vacuo. The solution was extracted with diethyl ether, dried with sodium sulfate, and filtered, and the solvent evaporated in vacuo. The residue was purified by flash chromatography (10−30% EtOAc in hexane) to yield 155 mg (44%) **43** as a white solid. Mp = 152−154 °C. ^{31}P NMR (162 MHz) δ 21.2 (q, J = 59 Hz). ^{1}H NMR (400 MHz) δ 0.6−1.7 (br m, 3H), 2.49 (br s, 1H), 4.49 (d, J = 6.1 Hz, 2H), 6.82−6.88 (m, 1H), 7.14−7.18 (m, 1H), 7.35−7.40 (m, 4H), 7.43−7.48 (m, 7H), 7.50−7.57 (m, 1H). ^{13}C NMR (100 MHz) δ 63.06 (d, J = 6.1 Hz), 127.37 (d, J = 12.2 Hz), 127.69 (d, J = 8.4 Hz), 128.76 (d, J = 58.7 Hz), 128.95 (d, J = 10.7 Hz), 130.97 (d, J = 9.1 Hz), 131.48 (d, J = 3.0 Hz), 131.93 (d, J = 3.0 Hz), 133.11 (d, J = 10.0 Hz), 134.01 (d, J = 6.1 Hz), 145.15 (d, J = 11.5 Hz).

Phosphinite borane **43** was converted to phosphine oxide **41.** A solution of 30 mg (0.10 mmol) of **36** in 1 mL of diethylamine was heated for 2 h at reflux. The diethylamine was evaporated in vacuo, and 5 mL of ether was added. To the solution was added 30 of mg *m*-CPBA, and the solution was stirred 1 h. The reaction mixture was wasted with 10% aqueous NaOH solution, dried over sodium sulfate, and filtered, and the solvent removed in vacuo to yield 30 mg (98%) of **41** as a white solid. ^{31}P NMR (121 MHz) δ 35.5. ^{1}H NMR (400 MHz) δ 4.58 (s, 2H), 5.79 (br s, 1H), 7.00−7.06 (m, 1H), 7.24−7.29 (m, 1H), 7.47−7.64 (m, 12H).

Endocyclic Restriction Test of 21 and 21-d_{12}. A mixture of 98.7 mg (0.23 mmol) of **21** and 86.4 mg (0.20 mmol) **21**-d_7 was prepared, and an aliquot was submitted for isotopic analysis (see Table 3). To a solution of 68.0 mg (0.16 mmol) of the above mixture dissolved in 2.0 mL of THF and cooled to −78 °C was added 240 μL (0.31 mmol) of 1.3 M *tert*-butyllithium, and the solution was stirred 5 min. The reaction mixture was quenched with water, and THF was removed in vacuo. The residue was dissolved in ether, washed with saturated aqueous NaCl solution, dried over sodium sulfate, and filtered, and solvent was removed in vacuo. The residue was purified by flash chromatography on silica (30% EtOAc in hexane) to yield 21.0 mg (44%) of phosphine borane **43**. ^{31}P NMR (162 MHz) δ 18.7 (m). ^{1}H NMR (400 MHz) δ 4.59 (s, 1H), 6.90−6.95 (m, 1H), 7.23−7.27 (m, 2H), 7.45−7.59 (m, 5H), 7.63−7.66 (m, 1H). A solution of 21.0 mg (0.07 mmol) of **43** in 1.0 mL of diethylamine was heated at reflux for 2 h. The diethylamine was evaporated in vacuo, and the residue was dissolved in 1 mL of diethyl ether. To the ethereal solution was added 25 mg of *m*-CPBA and stirred 30 min. The reaction mixture was washed with saturated aqueous Na_2CO_3 and brine, dried over sodium sulfate, and filtered, and the solvent was removed in vacuo to yield 14.6 mg (70%) of **51**. ^{31}P NMR (162 MHz) δ 35.54, 35.57. For isotopic analysis see Table 3.

Conversion of Phosphinite (*R*)-26 to Phosphine (*S*)-33. A solution of 0.11 M (*R*)-**26** in THF was prepared by adding 16 mL of THF to 824 mg (1.71 mmol) of (*R*)-**26**. A 4 mL aliquot (0.21 mmol) was removed and cooled to −78 °C. To this solution was added 330 μL (0.43 mmol) of 1.3 M *tert*-butyllithium. After 1 min the reaction was quenched and oxidized with 50 μL of 30% aqueous hydrogen peroxide solution. The THF was evaporated in vacuo, and ether was added. The solution was washed with saturated sodium bisulfite solution and brine, dried over magnesium sulfate, and filtered, and solvent removed in vacuo. The residue was purified by MPLC (50% to 100% EtOAc in hexane) to yield 33.0 mg (41%) phosphine oxide (*S*)-**33** as a colorless oil. ^{31}P NMR (162) δ 35.98. ^{1}H NMR (400 MHz) δ 3.07 (dt, J = 5.1, 8.8 Hz, 1H), 3.11 (dt, J = 5.1, 8.8 Hz, 1H), 3.92 (t, J = 5.5 Hz, 2H), 6.96−7.02 (m, 1H), 7.15−7.19 (m, 1H), 7.43−7.67 (m, 10H), 7.86−7.93 (m, 3H), 8.19 (d, J = 14.2 Hz, 1H). ^{13}C NMR (100 MHz) δ 37.21 (d, J = 4.6 Hz), 63.91, 125.76 (d, J = 3.7 Hz), 126.75 (d, J = 11.7 Hz), 127.05, 127.86, 128.50 (d, J = 21.4 Hz), 128.58 (d, J = 18.3 Hz), 128.80 (d, J = 25.9 Hz), 129.72, 130.56, 131.58 (d, J = 14.5 Hz), 131.63 (d, J = 9.2 Hz), 132.02 (d, J = 9.9 Hz), 132.17 (d, J = 2.3 Hz), 132.38 (d, J = 13.0 Hz), 132.75 (d, J = 2.3 Hz), 133.26, 133.39, 133.83 (d, J = 1.6 Hz), 134.73 (d, J = 2.3 Hz). FABMS *m/z* 107(19), 120(11), 136(66), 137(56), 138(32), 139(15), 154(100), 155-(26), 289(15), 307(26), 355(10), 373(97), 374(28). HRMS (FAB) *m/z* $(M + H)^+$ calcd 373.1357, obsd 373.1352.

Arbuzov Conditions for Conversion of (*R*)-26 to (*R*)-28. To a solution of 397 mg (0.82 mmol) of (*R*)-**26** in 1 mL THF was added 51 μL (0.82 mmol) of methyl iodide, and the solution was stirred for 16 h. The THF was evaporated in vacuo and purified by MPLC (EtOAc) to yield 177 mg (82%) of methylnaphthylphenylphosphine oxide (*R*)-**28**. Mp = 145−146 °C (lit.[31] Mp 146−147 °C). ^{31}P NMR (162 MHz) δ 30.66 ^{1}H NMR (400 MHz) δ 2.11 (d, J = 13.2 Hz, 3H), 7.45−7.66 (m, 6H), 7.74−7.79 (m, 2H) 7.86−7.94 (m, 3H), 8.36 (d, J = 13.4 Hz, 1H). EIMS (70 eV) *m/z* 267 (11), 266 (66), 265 (100), 251 (39), 127 (15), 77 (11). $[\alpha]_D$ = +13 ± 2° (*c* 1.34, MeOH). (lit. $[\alpha]_D$ = +12°).

Conditions for the Acylation of (*S*)-33. To a solution of 77 mg of (*S*)-**33** in 5 mL of dichloromethane was added 25 mg of DMAP, 33 μL of pyridine, and 30 μL of acetyl chloride. The solution was stirred 16 h. The reaction mixture was washed with 5% aqueous HCl solution, 5% aqueous NaOH solution, and brine, dried over magnesium sulfate, and filtered, and solvent evaporated in vacuo to afford (*S*)-**46**. No further purification was performed. ^{31}P NMR (162 MHz) δ 32.38. ^{1}H NMR (400 MHz) δ 1.95 (s, 3H), 3.26 (dt, J = 13.9, 7.1 Hz, 1H), 3.31 (dt, J = 13.9, 7.1 Hz, 1H), 4.18 (t, J = 7.1 Hz, 2H), 7.08−7.12 (m, 1H), 7.18−7.19 (m, 1H), 7.40−7.70 (m, 10H), 7.87−7.93 (m, 3H), 8.26 (d, J = 13.9 Hz, 1H). ^{13}C NMR (100 MHz) δ 20.95, 33.39 (d, J = 4.6 Hz), 64.41, 126.08 (d, J = 7.0 Hz), 126.81 (d, J = 10.7 Hz), 127.00, 127.86, 128.31, 128.50 (d, J = 16.8 Hz), 128.85 (d, J = 29.0 Hz), 129.27, 130.44 (d, J = 34.3 Hz), 131.64, 131.75, 131.94, 132.01, 132.04, 132.17, 132.32 (d, J = 15.2 Hz), 132.90 (d, J = 75.5 Hz), 133.89 (d, J = 12.9 Hz), 134.68 (d, J = 2.3 Hz), 143.23 (d, J = 8.4 Hz), 170.93. FABMS *m/z* 107(22), 120(14), 136(74), 137(62), 138-(33), 139(16), 154(100), 155(28), 289(13), 307(24), 355(19), 415(69), 416(22). HRMS (FAB) *m/z* $(M + H)^+$ calcd 415.1463, obsd 415.1463.

Determination of the Enantiomeric Ratio of (*S*)-38. Analyses were performed on a Rainin analytical HPLC system using a tandem silica column and Pirkle β-GEM column with 25% isopropyl alcohol in hexane at 1.25 mL/min.

Determination of the Enantiomeric Ratio of (*R*)-28. A solution of 15 mg (0.06 mmol) of **(*R*)-28** and 19 mg (0.06 mmol) of (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine in 500 μL of $CDCl_3$ was prepared and placed in a 5 mm NMR tube. The ^{31}P NMR spectrum was obtained at 162 MHz, and two peaks were observed.

Conversion of Phosphinate (*S*)-27 to Phosphine Oxide (*S*)-33. A solution of 0.10 M (*S*)-**27** in THF was prepared by dissolving 147 mg (0.30 mmol) of (*S*)-**27** in 3 mL of THF. A 1.5 mL (0.15 mmol) aliquot was removed and cooled to −78 °C. To this solution was added 310 μL (0.29 mmol) of 0.95 M *t*-butyllithium, and the solution was stirred 1 min. The reaction mixture was quenched with water, ether extracted, dried over magnesium sulfate, and filtered, and solvent evaporated in vacuo. The residue was purified by MPLC (50% to 100% EtOAc in hexane) to yield 7.5 mg (14%) (*S*)-**33**. ^{31}P NMR (162 MHz) δ 35.8. ^{1}H NMR (400 MHz) δ 3.08−3.11 (m, 2H), 3.90−3.93 (m, 2H), 6.97−6.99 (m, 1H), 7.02−7.05 (m, 1H), 7.42−7.68 (m, 10H), 7.86−7.93 (m, 3H), 8.20 (d, J = 14.0 Hz, 1H).

Typical Conditions for the Conversion of (*R*)-25 to (*S*)-33. A solution of 0.09 M (*R*)-**25** in THF was prepared by dissolving 657 mg (1.32 mmol) of (*R*)-**25** in 14 mL of THF. A 7 mL (0.66 mmol) aliquot was removed and cooled to −78 °C. To the solution was added 1.02 mL (1.32 mmol) of *t*-butyllithium, and the solution was stirred 1 min. The reaction mixture was quenched with water, and the THF evaporated in vacuo. The mixture was extracted with ether, dried over magnesium sulfate, and filtered, and solvent removed in vacuo. To the residue (*R*-)-**39** was added 10 mL of diethylamine, and the solution was heated to reflux for 2 h. The amine was removed in vacuo, and to the residue was added 10 mL of ether and 100 mg of 55% *m*-CPBA. The solution was stirred 0.5 h. The reaction mixture was washed with 5% aqueous NaOH solution and brine, dried over magnesium sulfate, and filtered and the solvent evaporated in vacuo. The residue was purified by MPLC (50% to 100% EtOAc in hexane) to yield 14.2 mg of (3%) (*S*)-**33**. ^{31}P NMR (162) δ 35.9.

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Supporting Information Available: The preparation of starting materials is listed (9 pages). See any current masthead page for ordering and Internet access instructions.

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