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Diastereoselective and Intramolecular Cycloadditions of Asymmetric *P*-Nitroso Phosphine Oxides

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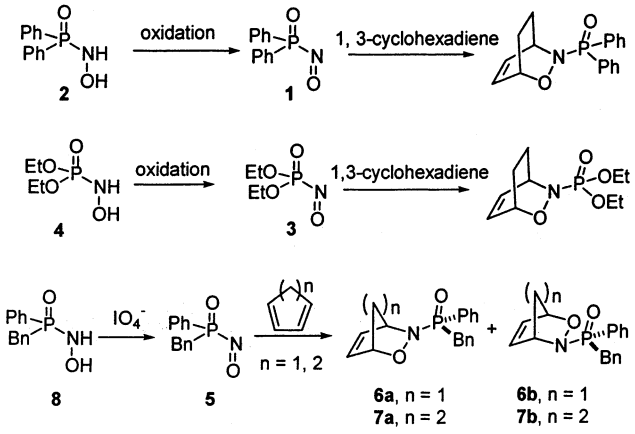
Benzyl phenyl *P*-nitroso phosphine oxide (**5**) reacts as an N−O heterodienophile with 1,3-cyclopentadiene to give the diastereomeric cycloadducts **6a,b** in a ratio of 1.5:1 (**6a:6b**). The same reaction in the presence of tin tetrachloride produces **6a,b** in a ratio of 2.9:1 (**6a:6b**). Cycloaddition of the structurally modified *P*-nitroso phosphine oxide (**18**) with 1,3-cyclopentadiene forms the diastereomeric cycloadducts **16a,b** in a ratio of 3.1:1 (**16a:16b**). These results suggest the reactions of these *P*-nitroso phosphine oxides and 1,3-cyclopentadiene occur through a transition state where the heterodienophile adopts an *s-cis* conformation and approaches the diene in an *exo* fashion *syn* to the phenyl group. This model resembles those proposed for the cycloadditions of the structurally similar asymmetric vinyl phosphine oxides. Reaction of **18** with 1,3-cyclopentadiene in the presence of a Lewis acid produces cycloadducts **16a,b** in a ratio of 7:1 (**16a:16b**), which approaches synthetic utility. Similar experiments show that 1,3-cyclohexadiene likely reacts with *P*-nitroso phosphine oxides through a different transition state, limiting current predictions regarding the diastereoselectivity of these reactions. The intramolecular cycloaddition of an asymmetric *P*-nitroso phosphine oxide (**19**) for the first time produces a unique phosphorus-containing heterocyclic compound (**20**).

Introduction

P-Nitroso phosphine oxides (**1**, *N*-phosphinoylnitroso compounds), produced from the oxidation of the corresponding *N*-hydroxyphosphinamides (**2**, *N*-phosphinoylhydroxylamines), react with many 1,3-dienes to produce new phosphorus-containing cycloadducts (Scheme 1).[1] This unique reaction introduces oxygen, nitrogen and phosphorus atoms into hydrocarbon 1,3-dienes in a single step.[1] Reduction of the N−O bond of these compounds also forms highly functionalized *cis*-1,4-phosphinamido allylic alcohols.[1] Similarly, *P*-nitroso phosphate intermediates (**3**), produced from the oxidation of the corresponding *N*-hydroxyphosphoramidates (**4**, Scheme 1), react with 1,3-dienes as N−O heterodienophiles.[2] Benzyl phenyl *P*-nitroso phosphine oxide (**5**), which is asymmetric at P, reacts with cyclic 1,3-dienes to give the diastereomeric cycloadducts (**6a,b** and **7a,b**, Scheme 1) with the relative stereochemistry of the major cycloadducts (**6a** and **7a**) being determined by single-crystal X-ray crystallography.[1] Initial analytical HPLC analysis indicates that **6a** and **7a** preferentially form in greater than a 20:1 ratio to **6b** and **7b** in these reactions.[1]

Transition state models to explain this observed diastereoselectivity must address several issues including *endo* vs *exo* approach of the dienophile to the diene, *s-cis* vs *s-trans* conformation of the dienophile, and the steric

SCHEME 1



interactions between the diene and dienophile. Assuming a planar conformation of the N═O and P═O groups in the dienophile to maximize orbital overlap, four possible transition states could produce the major observed diastereomers (**6a**, **7a**) in these reactions (Figure 1). In transition state A (shown with 1,3-cyclopentadiene), the dienophile approaches the diene in an *exo* fashion and in an *s-cis* conformation on the same face as the phenyl group. In transition state B, the dienophile approaches the diene in an *exo* orientation in an *s-trans* conformation on the same face as the benzyl group. Transition state C is characterized by the dienophile in the *s-trans* conformation approaching the diene in an *endo* fashion on the same face as the phenyl group. Finally, in transition state D, the dienophile approaches the diene in an *endo*

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(1) Ware, R. W., Jr.; King, S. B. *J. Am. Chem. Soc.* **1999**, *121*, 6769−6770.

(2) Ware, R. W., Jr.; King, S. B. *J. Org. Chem.* **2000**, *65*, 8725−8729.

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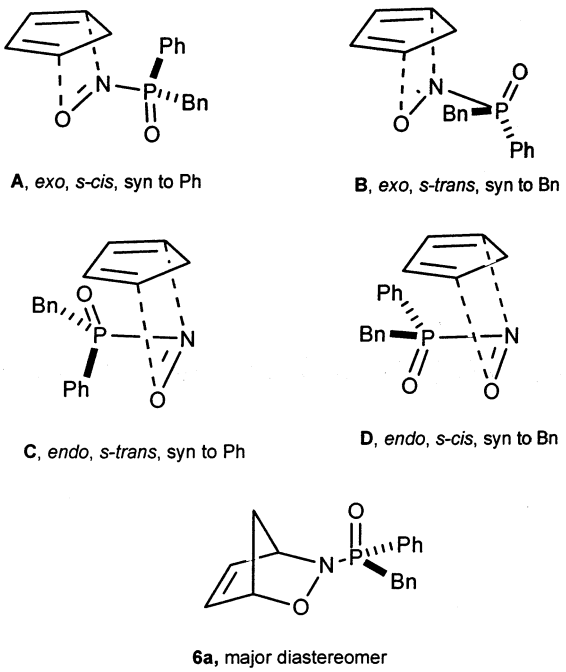


FIGURE 1. Possible transition state structures for the formation of the major diastereomer **6a**.

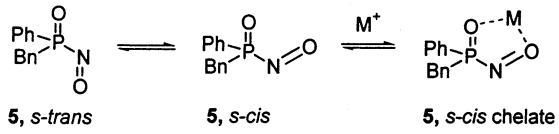


FIGURE 2. The *s-trans*, *s-cis*, and *s-cis* Lewis acid chelated conformations of the *P*-nitroso phosphine oxide (**5**).

orientation in a *s-cis* conformation on the same side as the benzyl group.

Experiments using Lewis acids and structurally modified *P*-nitroso phosphine oxides should indicate a preferred transition state geometry for these reactions. Lewis acids should form five-membered ring chelate complexes with *P*-nitroso phosphine oxides such as **5** and stabilize the *s-cis* conformation of transition states A and D (Figures 1 and 2).[3] Enhancement of the diastereoselectivity of these reactions in the presence of Lewis acids would indicate the preference of the *s-cis* conformation and eliminate transitions state structures B and C (Figures 1 and 2). Increasing the size of the benzyl group should facilitate approach of the diene from the side *syn* to the phenyl group. An increase in the ratio of diastereomers upon increasing the size of the benzyl group would indicate that approach of the diene *syn* to the phenyl group was favored and transition states B and D (Figure 1) could be eliminated. The combination of the results of these experiments should indicate which transition state model gives rise to the major observed diastereomers (**6a**, **7a**). Here we describe experiments with Lewis acids and structurally modified *P*-nitroso phosphine oxides to discriminate between these possible transition state models and provide a better understanding of the diastereoselectivity of these reactions. In addition, we also describe the first example of an intramolecular cycloaddition of an asymmetric *P*-nitroso phosphine oxide.

(3) (a) Zhang, Y.; Flann, C. J. *J. Org. Chem.* **1998**, *63*, 1372−1378. (b) Remiszewski, S. W.; Yang, J.; Weinreb, S. M. *Tetrahedron Lett.* **1986**, *27*, 1853−1856. (c) Whitesell, J. K.; James, D.; Carpenter, J. F. J. *Chem. Soc., Chem. Commun.* **1985**, 1449−1450.

TABLE 1. Effects of Lewis Acids on Diastereoselectivity of Cycloadditions of 5 with 1,3-Cyclopentadiene and 1,3-Cyclohexadiene

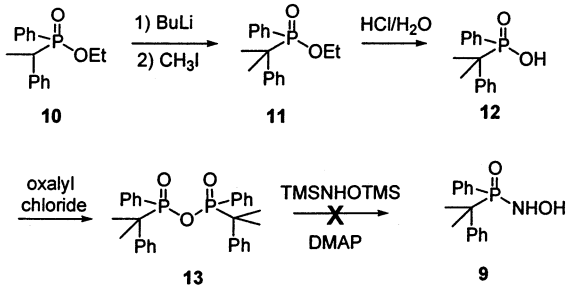
Lewis acid	**6a**:**6b**	**7a**:**7b**
none	1.5:1	1.7:1
$SnCl_4$	2.6:1	1.7:1
$TiCl_4$	2.9:1	1.5:1

Results

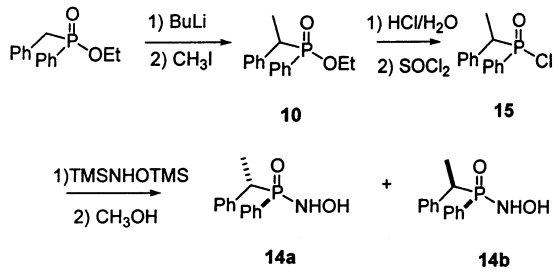
Periodate oxidation of benzyl phenyl *N*-hydroxyphosphinamide (**8**) at 0 °C in the presence of 1,3-cyclopentadiene or 1,3-cyclohexadiene produces diastereomeric cycloadducts **6a,b** and **7a,b** in 85% and 87% yield, respectively (Scheme 1).[1] The isolation and characterization of cycloadducts **6a,b** and **7a,b** provides further support for the intermediacy of *P*-nitroso phosphine oxides.[1] Phosphorus nuclear magnetic resonance (NMR) measurements of these crude reaction mixtures show that **6a** ($\delta = 39.6$ ppm) and **7a** ($\delta = 38.0$ ppm) preferentially form in a 1.5:1 and 1.7:1 ratio to **6b** ($\delta = 38.2$ ppm) and **7b** ($\delta = 39.0$ ppm), respectively. Incubation of pure **6a** or **7a** under reaction conditions does not result in equilibration to mixtures of **6a,b** or **7a,b**, indicating that these diastereomers form under kinetic conditions. These results markedly differ from our earlier report that **6a** and **7a** preferentially form over **6b** and **7b** in greater than a 20:1 ratio.[1] The drastic difference in these measurements appears to result from the fact that the earlier measurements relied upon analytical HPLC, which required the sample to be prepurified by a short silica gel column to remove the tetrabutylammonium salt byproducts. Apparently, this chromatography resulted in the enrichment of **6a** and **7a** in these samples and subsequent control experiments show that the ratio of **6/7a**:**6**/**7b** changes after silica gel chromatography. In contrast, phosphorus NMR, which detects only molecules that contain P, can be directly utilized on unpurified reaction samples, allowing for the confident and accurate determination of the product ratio. Because of these attributes, phosphorus NMR represents the method of choice for determining the product ratio of these reactions and was used to determine product ratios in each of the subsequently described experiments.

Oxidation of **8** at 0 °C in methylene chloride in the presence of 1 equiv of a Lewis acid ($SnCl_4$ or $TiCl_4$) and 1,3-cyclopentadiene or 1,3-cyclohexadiene also produces the diastereomeric cycloadducts **6a,b** and **7 a,b** in yields similar to those of the reactions in the absence of Lewis acid. Table 1 summarizes the effect of these Lewis acids on the diastereoselectivity of these cycloadditions as determined by phosphorus NMR measurements of these crude reaction mixtures. For the cycloaddition of **5** with 1,3-cyclopentadiene, the addition of a Lewis acid nearly doubles the diastereomeric ratio of **6a**:**6b** (Table 1) with **6a** remaining as the major product. Surprisingly, the addition of a Lewis acid to the reaction of **5** with 1,3-cyclohexadiene did not influence the ratio of diastereomers **7a** and **7b** (Table 1).

SCHEME 2



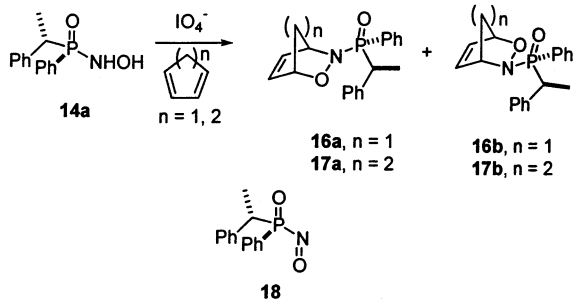
SCHEME 3



Initially, the dimethyl *N*-hydroxyphosphinamide (**9**, Scheme 2) was chosen as a structural probe for determining the preferred approach of the diene to the corresponding *P*-nitroso phosphine oxide in these reactions. Treatment of the known phosphinic ester (**10**) with butyllithium followed by methyl iodide produces the phosphinic ester (**11,** Scheme 2).[4] Acid hydrolysis gives the corresponding phosphinic acid (**12**, Scheme 2). Refluxing **12** in thionyl chloride failed to produce the desired phosphinic chloride but formed the anhydride (**13**) as determined by proton and phosphorus NMR and single-crystal X-ray crystallography.[5] Treatment of **12** with oxalyl chloride also produced **13**, indicating that the increased steric hindrance surrounding the phosphorus atom favors formation of **13** over the desired phosphinic chloride. Treatment of **13** with *N*,*O*-bis(trimethylsilyl)-hydroxylamine (TMSNHOTMS) and DMAP, the standard procedure for converting phosphinic chlorides to *N*-hydroxyphosphine oxides,[6] also failed to produce **9**.

The inability to produce **9** focused our attention on the diastereomeric monomethyl *N*-hydroxyphosphinamides (**14a** and **14b**, Scheme 3). Previous work showed that **14a** and **14b** can be separated through precipitation and recrystallization.[4] Thus, treatment of ethyl (benzyl)-phenyl phosphinate with *n*-butyllithium followed by methyl iodide produced the phosphinic ester (**10**) as a mixture of diastereomers in 67% yield (Scheme 3). Acidic hydrolysis followed by exposure to thionyl chloride gives (benzyl)phenyl phosphinic chloride (**15**) also as a mixture of diastereomers (Scheme 3).[4] Addition of TMSNHOTMS to this phosphinic chloride produces the O-TMS-protected derivatives of **14a** and **14b** as a solid material enriched in a single diastereomer.[4] Methanolysis of the O-TMS group followed by recrystallization yields a single *N*-hydroxyphosphinamide as judged by ^{31}P NMR (δ = 41.1 ppm, Scheme 3). This material demonstrates proton and phosphorus NMR spectra identical to those previously reported for this compound.[4] Single-crystal X-ray crystallographic studies of the subsequent products of the oxidation of this *N*-hydroxyphosphinamide in the presence of 1,3-cyclohexadiene reveal that the relative stereochemistry of this compound corresponds to that shown for **14a** (vide infra).

SCHEME 4



Periodate oxidation of **14a** at 0 °C in the presence of 1,3-cyclopentadiene or 1,3-cyclohexadiene produces diastereomeric cycloadducts **16a,b** and **17a,b** in 65% and 64% yield, respectively (Scheme 4). Phosphorus NMR measurements of these crude reaction mixtures show that **16a** (δ = 42.5 ppm) and **17a** (δ = 41.6 ppm) preferentially form in a 3.1:1 and 3.5:1 ratio to **16b** (δ = 41.4 ppm) and **17b** (δ = 41.4 ppm), respectively. These results provide evidence for the intermediacy of the *P*-nitroso phosphine oxide **18** (Scheme 4). The relative stereochemistry of the major diastereomer of **17a** was determined by single-crystal X-ray crystallography, which confirms the relative stereochemistry of **14a** (Scheme 3).[7] Oxidation of **14a** at 0 °C in methylene chloride in the presence of one equivalent of $SnCl_4$ and 1,3-cyclopentadiene also produces the diastereomeric cycloadducts **16a,b** in a 7:1 ratio of **16a**:**16b** as determined by phosphorus NMR.

Generation of a *P*-nitroso phosphine oxide in a structure containing an accessible 1,3-diene group should produce unique decalin-like structures through an intramolecular cycloaddition. Thus, our efforts focused on the *P*-nitroso phosphine oxide (**19**) as a precursor for the phosphorus-, nitrogen-, and oxygen-containing bicyclic heterocycle (**20**, Scheme 5). Lithium aluminum hydride reduction of ester (**21**) produces the dienyl alcohol in 86% yield (**22**, Scheme 5).[8] Conversion of **22** to the tosylate (**23**) and bromide (**24**) under standard conditions occurs in 69% and 96% yield, respectively (Scheme 5).[9,10] Treatment of **24** with diethyl phenylphosphonite gives the phosphinic ester (**25**) in 63% yield, and basic hydrolysis

(4) Harger, M. J. P.; Sreedharan-Menon, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3261−3267.

(5) Crystal data for **13**·CH_2Cl_2: $C_{31}H_{34}Cl_2O_3P_2$, monoclinic, *C*2/*c*-C^6_{2h}, colorless crystal, a = 15.785(2) Å, b = 10.882(1) Å, c = 17.098(2) Å, β = 100.29(1)°, volume = 2889.8(6) Å ^{3}, Z = 4, R_1 = 0.076, wR_2 = 0.106, GOOF = 1.012, data/parameters = 2948/175.

(6) Harger, M. J. P.; Shimmin, P. A. *Tetrahedron* **1992**, *48*, 7539−7550.

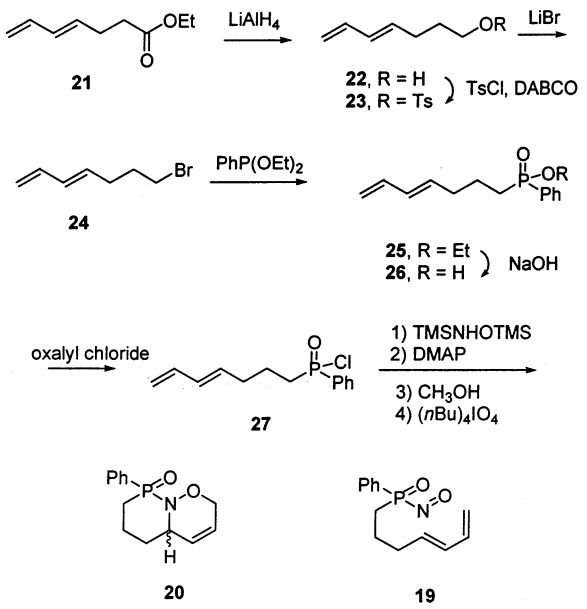
(7) Crystal data for **17a**: $C_{20}H_{22}NO_2P$, triclinic, $P\bar{1}$-C^1_i, colorless crystal, a = 8.447(1) Å, b = 10.064(2) Å, c = 11.698(2) Å, α = 70.48-(1)°, β = 69.67(1)°, γ = 76.69(1)°, volume = 871.6(2) Å^3, Z = 2, R_1 = 0.0481, wR_2 = 0.0990, GOOF = 1.029, data/parameters = 3928/218.

(8) Raederstorff, D.; Shu, A. Y. L.; Thompson, J. E.; Djerrassi, C. *J. Org. Chem*. **1987**, *52*, 2337−2346.

(9) Hartung, J.; Hunig, S.; Kneuer, R.; Schwarz, M.; Wenner, H. *Synthesis* **1997**, 1433−1438.

(10) Wilt, J. W.; Massie, S. N.; Dabek, R. B. *J. Org. Chem*. **1970**, *35*, 2803−2806.

SCHEME 5



yields the phosphinic acid (**26**, 98% yield, Scheme 5).[11] Exposure of **26** to *N*,*N*-diethyl(trimethylsilyl) amine followed by chlorination with oxalyl chloride and catalytic amounts of DMF produces the desired phosphinic chloride (**27**), which was used without further purification (Scheme 5).[12] Simply using oxalyl or thionyl chloride for the conversion of phosphinic acid (**26**) to phosphinic chloride (**27**) proved to be particularly problematic, presumably as a result of acid-catalyzed reactions of the 1,3-diene functionality. Treatment of **27** with TMSNHOTMS in the presence of DMAP followed by the in situ methanolysis of the O-TMS-protected hydroxylamine in the presence of tetra *n*-butylammonium periodate produces (**20**) in 51% yield (based upon **27**, Scheme 5). Phosphorus NMR experiments of the crude reaction mixture show a single peak indicating the formation of a single diastereomer ($\delta = 29.7$ ppm). At the present time, compound **20** has not succumbed to our efforts at crystallization for single-crystal X-ray diffraction studies and two-dimensional NMR correlation experiments fail to conclusively demonstrate the relative stereochemistry. However, these results strongly support the intermediacy of the *P*-nitroso phosphine oxide (**19**) in this sequence.

Discussion

The isolation and characterization of cycloadducts **6a,-6b**/**7a,7b** and **16a,16b**/**17a,17b** provide strong evidence for the intermediacy of the *P*-nitroso phosphine oxides **5** and **18** in these reactions (Schemes 1 and 4). Phosphorus NMR experiments show that **5** diastereoselectively reacts with 1,3-cyclopentadiene and 1,3-cyclohexadiene to give a modest excess of **6a**/**7a** over **6b**/**7b**. The small ratio of **6a/7a**:**6b/7b** likely reflects a lack of selectivity for the approach of the diene to **5** from a specific face, which is somewhat surprising given the relatively larger size of a phenyl group compared to a benzyl group.[13] Also, a previously reported Diels−Alder reaction of an asymmetric benzyl phenyl substituted vinyl phosphine oxide occurred from the side of the benzyl group.[14] However, benzyl phenyl vinyl phosphine oxide itself undergoes 1,3-dipolar cycloadditions with nitrones with little diastereoselectivity.[15] X-ray crystallographic studies provide the relative stereochemistry of these products and also reveal that the major cycloadducts (**6a**, **7a**, **16a**, and **17a**) share the same relative stereochemistry.

Addition of a Lewis acid to the reaction of **5** with 1,3-cyclopentadiene increases the diastereoselectivity of the cycloaddition with **6a** remaining the major product. This increase in diastereoselectivity suggests that this reaction proceeds through a transition state in which the dienophile adopts an *s-cis* conformation (A or D, Figure 1) and that the Lewis acid may be stabilizing the *s-cis* conformation by forming a five-membered ring chelate complex. Previous work shows that Lewis acids enhance the diastereoselectivity of the hetero Diels−Alder reactions of both *N*-sulfinylphosphoramidates and *N*-sulfinylcarbamates.[3] Each of these studies also propose that the source of the improved diastereoselectivity arises from the ability of the Lewis acid to organize the heterodienophile through chelation.[3] Increasing the size of the benzyl group of **5** by the addition of a methyl group to yield **18** also increases the diastereoselectivity of this reaction with **16a** being the major product that possesses the same relative stereochemistry as **6a**. These results suggest that the diene approaches *syn* to the phenyl group of **5** and **18** in this reaction and that this reaction proceeds through either transition state A or C (Figure 1). Combining the results from both of these experiments identifies transition state model A as the most likely transition state for the reactions of **5** and **18** with 1,3-cyclopentadiene. In this model, the *P*-nitroso phosphine oxide approaches the diene in an *s-cis* conformation, in an *exo* fashion and *syn* to the phenyl group (Figure 1). The further increase in diastereoselectivity upon the addition of a Lewis acid to the reaction of **18** with 1,3-cyclopentadiene further supports model A as the transition state structure in these cycloadditions. The 7:1 ratio of **16a**:**16b** produced under these conditions approaches a synthetically useful level and encourages the further development of new and chiral *P*-nitroso phosphine oxides.

Previous work with structurally similar vinyl phosphine oxides as dienophiles supports the proposed transition state model. The Diels−Alder reaction of 1,3-cyclopentadiene with methyl phenyl vinyl phosphine oxide produces the *exo* cycloadduct as the major product.[16] Other asymmetric vinyl phosphine oxides also undergo Diels−Alder reactions with the phosphine oxide group in the *exo* orientation.[14] Vinyl phosphine oxides also prefer to adopt the *s-cis* conformation, and the addition of Lewis acids enhances the diastereoselectivity of the reaction of methyl phenyl vinyl phosphine and 1,3-

(11) Allen, C. F.; Kalm, M. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 616.
(12) Biller, S. A.; Forster, C. *Tetrahedron Lett*. **1990**, *46*, 6645−6648.
(13) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; p 697.
(14) Bodalski, R.; Koszuk, J.; Krawczyk, H.; Pietrusiewicz, K. M. *J. Org. Chem*. **1982**, *47*, 2219−2220.
(15) Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M.; Zablocka, M.; Wisniewski, W. *J. Org. Chem*. **1991**, *56*, 4383−4388.
(16) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev*. **1994**, *94*, 1375−1411.

cyclopentadiene, suggesting reaction through the *s-cis* conformation.[16,17] Acyl nitroso compounds also bear some structural similarity to the *P*-nitroso phosphine oxides and act as N−O heterodieneophiles. While a number of asymmetric acyl nitroso compounds exist that give moderate to high levels of diastereoselectivity in cycloadditions, no general transition state model currently exists for these reactive species.[18,19]

The diastereoselectivity of cycloaddition also increases during the reaction of **18** with 1,3-cyclohexadiene as compared to the reaction of **5** with 1,3-cyclohexadiene. Like the results with 1,3-cyclopentadiene, this result suggests that 1,3-cyclohexadiene approaches these heterodienophiles from the side *syn* to the phenyl group (A or C, Figure 1). In contrast to the reaction of **5** with 1,3-cyclopentadiene, the addition of a Lewis acid to the reaction of **5** and 1,3-cyclohexadiene had no effect on the diastereoselectivity. Again, X-ray crystallographic studies indicate that the relative stereochemistry of the major cycloadduct remains the same in the Lewis acid experiments. While the inability of a Lewis acid to alter the diastereoselectivity of this process suggests that **5** reacts with 1,3-cyclohexadiene in an *s-trans* conformation (specifically transition state model C, Figure 1), it is presently not clear why such a small structural change in the diene dramatically influences both the conformation and approach of the dienophile. While the reaction of **5** with 1,3-cyclopentadiene follows the reaction pattern of the structurally similar asymmetric vinyl phosphine oxides, the results with 1,3-cyclohexadiene immediately indicate that further experiments with more dienes will be required for the development of a general model to describe the stereochemistry of these cycloadditions.

P-Nitroso phosphine oxide (**19**) reacted intramolecularly with an internal 1,3-diene to form the decalin derivative (**20**) in the first described intramolecular *P*-nitroso phosphine oxide cycloaddition. Compound **20** contains an asymmetric cyclic phosphorus atom and the unusual structural feature of contiguous phosphorus, nitrogen, and oxygen atoms in a bicyclic ring system. Similar ring systems formed by the intramolecular cycloadditions of acyl nitroso compounds have been converted into various nitrogen-containing compounds including retronecine,[20] swainsonine,[21] lepadin B,[22] (+)-loline,[23] and cephalotaxus.[24] Similar synthetic manipulations of **20** or other intramolecular *P*-nitroso phosphine oxide cycloadducts could conceivably produce asymmetric phosphorus-containing analogues of these biologically active molecules. Further experiments will be designed to improve the synthesis and determine the relative stereochemistry of **20** and to explore the synthetic conversion of cycloadducts, like **20**, into more complex and unique phosphorus containing molecules.

In summary, asymmetric *P*-nitroso phosphine oxides react with 1,3-cyclopentadiene and 1,3-cyclohexadiene to give mixtures of products enriched in a single diastereomer. Experiments with Lewis acids and structurally modified *P*-nitroso phosphine oxides show that in the reaction with 1,3-cyclopentadiene these heterodienophiles approach the diene in an *s-cis* conformation in an *exo* orientation and *syn* to the phenyl group. Such a transition state model is similar to previous results with asymmetric vinyl phosphine oxides. Reaction of the *P*-nitroso phosphine oxide (**18**) with 1,3-cyclopentadiene in the presence of a Lewis acid results in a 7:1 ratio of diastereomers. However, similar experiments indicate that 1,3-cyclohexadiene likely reacts in a different transition state geometry than 1,3-cyclopentadine, limiting any current predictions regarding the diastereoselectivity of these reactions. On the basis of these limited results, the transition state model may or may not be applicable to open chain dienes. Intramolecular cycloaddition of an asymmetric *P*-nitroso for the first time produces unique phosphorus-containing heterocyclic compounds. Taken together, these results support the further development of chiral asymmetric *P*-nitroso phosphine oxides as new synthetic reagents and intermediates for the synthesis of complex phosphorus containing molecules.

Experimental Section

General. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F-254 precoated plates. Flash chromatography was performed on silica gel 60 (230−400 mesh). ^{1}H NMR spectra were taken in commercial deuterated solvents on a multinuclear spectrometer with all chemical shifts being reported in δ scale in parts per million from Me_4Si. ^{13}C NMR spectra were taken on a multinuclear spectrometer (75 MHz). ^{31}P NMR spectra were taken on a multinuclear spectrometer (121 MHz) and referenced to H_3PO_4 (defined as 0 ppm). Organic solvents were distilled from a drying agent prior to use. Commercially available reagents were used without further purification. The preparation and characterization of ethyl benzyl phenyl phosphinate, compounds **6a,b**, **7a,b**, and **8** have been previously described.[1]

(1-Methyl-1-phenylethyl)(phenyl)phosphinic Acid Ethyl Ester (11). Phenyl-(1-phenylethyl)phosphinic acid ethyl ester (**10**)[4] (0.342 g, 1.25 mmol) was dissolved in tetrahydrofuran (15 mL) and cooled to −78 °C in a dry ice−acetone bath under an atmosphere of argon. *n*-Butyllithium (0.857 mL, 1.37 mmol) was added dropwise over a 45-min period via a syringe pump and stirred for 1 h. Methyl iodide (0.155 mL, 2.50 mmol) was added dropwise over a 45-min period and stirred for 18 h at 23 °C. Methylene chloride (20 mL) was added to the reaction mixture, and this mixture was extracted with brine (2 × 25 mL), dried over magnesium sulfate, and concentrated in vacuo to afford a solid. The crude product was purified by silica gel chromatography (1:1, EtOAc/pentane) to yield **11** as a white solid (0.240 g, 67%): mp 53−54 °C; R_f 0.22 (1:1, EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.18 (m, 10H), 4.09−3.99 (m, 1H), 3.92−3.79 (m, 1H), 1.60 (t, 6H, J = 14.7 Hz), 1.28 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.9−129.1 (m, aromatic), 63.7 (d, 1C, J = 7.2 Hz), 43.3 (d, 1C, J = 93.6 Hz), 25.7 (d, 1C, J = 1.6 Hz), 25.6, 19.0 (d, 1C, J = 7.0 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 47.9; IR ($CDCl_3$) 1204, 1034 cm^{-1}; LRMS (ESI) m/z 311 (M + Na)$^+$. Anal. Calcd for $C_{17}H_{21}O_2P$: C, 70.82; H, 7.34. Found: C, 70.08; H, 7.37.

(1-Methyl-1-phenylethyl)(phenyl)phosphinic Acid (12). (1-Methyl-1-phenylethyl)(phenyl)phosphinic acid ethyl ester

(17) Pietrusiewicz, K. M.; Zablocka, M.; Wieczorek, W.; Brandi, A. *Tetrahedron: Asymmetry* **1991**, *2*, 419−428.
(18) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348.
(19) (a) Gouverneur, V.; Ghosez, L. *Tetrahedron: Asymmetry* **1990**, *1*, 363−366. (b) Gouverneur, V.; Ghosez, L. *Tetrahedron Lett.* **1991**, *39*, 5349−5352. (c) Gouverneur, V.; Dive, G.; Ghosez, L. *Tetrahedron: Asymmetry* **1991**, *2*, 1173−1176.
(20) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632−3634.
(21) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083−6089.
(22) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955−2958.
(23) Blakemore, P. R.; Schulze, V. K.; White, J. D. *Chem. Comm.* **2000**, 1263−1264.
(24) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341−2342.

(**11**) (0.220 g, 0.763 mmol) was refluxed in concentrated HCl (5 mL) for 18 h. The mixture was diluted with water (20 mL), extracted with methylene chloride (4 × 20 mL), dried over magnesium sulfate, and concentrated in vacuo. The resulting solid was recrystallized (1:1, methylene chloride/hexanes) to yield **12** as a white solid (0.161 g, 81%): mp 129−130 °C; R_f 0.19 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.9 (s, 1H), 7.40−7.16 (m, 10H), 1.49 (d, 6H, J = 15.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.4−126.3 (m, aromatic), 40.5 (d, 1C, J = 93.4 Hz), 22.7; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 50.0; IR ($CDCl_3$) 3160−2489 (br OH) cm^{-1}; LRMS (ESI) m/z 261 (M + H)$^+$. Anal. Calcd for $C_{15}H_{17}O_2P$: C, 69.22; H, 6.58. Found: C, 68.75; H, 6.66.

(1-Methyl-1-phenylethyl)(phenyl)phosphinic Anhydride (13). Phosphinic acid (**12**) was stirred with oxalyl chloride (0.571 g, 4.50 mmol) in anhydrous methylene chloride (5 mL) for 2 days. The reaction mixture was concentrated in vacuo and purified by silica gel chromatography (EtOAc) to afford **13** as a white solid: R_f 0.66 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.17 (m, 20H), 1.63−1.53 (m, 12H); ^{31}P NMR ($CDCl_3$, 122 MHz) δ 46.3.

***N*-[Phenyl-(1-phenylethyl)phosphinoyl]hydroxylamine (14a).** *N*,*O*-Bis(trimethylsilyl)hydroxylamine (2.26 g, 12.8 mmol) was added dropwise to a stirred solution of phenyl-(1-phenylethyl)phosphinic chloride (**15**)[4] (2.60 g, 9.82 mmol) in anhydrous methylene chloride (20 mL) under an atmosphere of argon and stirred for 2 h at 0 °C. The reaction was warmed to room temperature for 16 h during which time a white solid precipitated. The solid was filtered, washed with diethyl ether, and dried in vacuo. Crude ^{1}H NMR indicated that the white solid was the *O*-(TMS)hydroxylamine and it was used without further purification. The *O*-(TMS)hydroxylamine (2.02 g) was dissolved in a solution of anhydrous methylene chloride (20 mL) containing anhydrous methanol (1.50 mL) and stirred at room temperature for 3 days to afford a mixture of diastereomers **14a** and **14b**. Recrystallization of the diastereomeric mixture from methylene chloride produced **14a** (1.12 g, 64%): R_f 0.47 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68−7.51 (m, 2H), 7.48−7.39 (m, 1H), 7.36−7.27 (m, 2H), 7.20−6.99 (m, 5H), 3.34−3.21 (m, 1H), 1.31 (dd, 3H, J_{PH} = 16.6 Hz, J_{HH} = 7.3 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 41.1.

3-[Phenyl-(1-phenylethyl)phosphinoyl]-2-oxa-3-azabicyclo[2.2.1]oct-5-ene (16a and 16b). A solution of **14a** (0.172 g, 0.660 mmol) in anhydrous methylene chloride (5 mL) was added dropwise to a cooled (0 °C), stirred solution of tetra *n*-butylammonium periodate (0.314 g, 0.726 mmol) and 1,3-cyclopentadiene (0.087 g, 1.32 mmol) in anhydrous methylene chloride (10 mL) under an argon atmosphere and stirred for 2 h. The reaction was warmed to room temperature and stirred an additional 6 h and concentrated in vacuo. Phosphorus NMR of the crude reaction mixture indicated that diastereomers **16a** and **16b** were formed in a 3.1:1 ratio. The two diastereomers were separated by flash chromatography (3:1, EtOAc/pentane) to yield compounds **16a** and **16b** (0.140 g, 65%) as clear viscous oils. **Data for 16a**: R_f 0.34 (3:1 EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70−7.55 (m, 2H), 7.48−7.43 (m, 1H), 7.39−7.30 (m, 2H), 7.19−7.08 (m, 5H), 6.12−6.11 (m, 2H), 5.11 (br s, 1H), 4.29 (br s, 1H), 3.65−3.43 (m, 1H), 2.14−1.96 (m, 2H), 1.39 (dd, 3H, J_{PMe} = 17.3 Hz, J_{HMe} = 7.5 Hz), 1.23−1.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4−127.2 (m, aromatic and alkene), 83.2, 64.2 (d, 1C, J = 4.3 Hz), 48.9 (d, 1C, J = 2.3 Hz), 41.3 (d, 1C, J = 87.1 Hz), 16.3; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 42.5; IR ($CDCl_3$) 1198, 1009 cm^{-1}; LRMS (ESI) m/z 326 (M + H)$^+$. Anal. Calcd for $C_{19}H_{20}NO_2P$: C, 70.14; H, 6.20; N, 4.31. Found: C, 70.44; H, 6.57; N, 3.38. **Data for 16b**: R_f 0.24 (3:1 EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86−7.56 (m, 2H), 7.49−7.24 (m, 3H), 7.19−7.08 (m, 5H), 6.21−6.20 (m, 2H), 5.01 (br s, 1H0, 4.01 (br s, 1H), 3.51−3.37 (m, 1H), 1.91−1.89 (m, 1H), 1.46 (dd, 3H, J_{PMe} = 20.7 Hz, J_{HMe} = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.7−127.0 (m, aromatic and alkene), 70.3, 49.0 (d, 1C, J = 2.4 Hz), 40.5 (d, 1C, J = 86.8 Hz), 24.3, 23.1 (d, 1C, J = 11.6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 41.4; IR ($CDCl_3$) 1198, 1009 cm^{-1}; LRMS (ESI) m/z 326 (M + H)$^+$. Anal. Calcd for $C_{19}H_{20}NO_2P$: C, 70.14; H, 6.20; N, 4.31. Found: C, 68.28; H, 7.00; N, 3.44.

3-[Phenyl-(1-phenylethyl)phosphinoyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (17a and 17b). A solution of **14a** (0.138 g, 0.531 mmol) dissolved in anhydrous methylene chloride (5 mL) was added dropwise to a cooled (0 °C), stirred solution of tetra *n*-butylammonium periodate (0.253 g, 0.584 mmol) and 1,3-cyclohexadiene (0.085 g, 1.06 mmol) in anhydrous methylene chloride (10 mL) under an argon atmosphere and stirred for 2 h. The reaction was warmed to room temperature and stirred an additional 6 h and concentrated in vacuo. Phosphorus NMR of the crude reaction mixture indicated that diastereomers **17a** and **17b** were formed in a 3.5:1 ratio. The two diastereomers were separated by flash chromatography (3:1, EtOAc/pentane) to yield compounds **17a** and **17b** (0.115 g, 64%) as clear viscous oils. **Data for 17a**: R_f 0.34 (3:1 EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73−7.67 (m, 2H), 7.45−7.13 (m, 8H), 5.93−5.83 (m, 2H), 4.43−4.40 (m, 1H), 3.99 (br s, 1H), 3.61−3.53 (sextet, 1H, J = 7.5 Hz), 2.10−2.02 (m, 1H), 1.87−1.79 (m, 1H), 1.24 (dd, 3H, J_{PMe} = 18.1 Hz, J_{HMe} = 7.6 Hz), 1.23−1.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4−127.0 (m, aromatic and alkene), 70.1, 47.7 (d, 1C, J = 3.5 Hz), 38.0 (d, 1C, J = 89.0 Hz), 24.4, 22.9 (d, 1C, J = 9.7 Hz), 14.7; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 41.6; IR ($CDCl_3$) 1197, 1110, 1060 cm^{-1}; LRMS (ESI) m/z 340 (M + H)$^+$. Anal. Calcd for $C_{20}H_{22}NO_2P$: C, 70.78; H, 6.53; N, 4.13. Found: C, 69.78; H, 6.77; N, 3.94. **Data for 17b**: R_f 0.18 (3:1 EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59−7.56 (m, 2H), 7.48−7.43 (m, 1H), 7.35−7.29 (m, 2H), 7.09−7.07 (m, 3H), 6.94−6.92 (m, 2H), 6.51−6.40 (m, 2H), 4.61−4.60 (m, 1H), 3.80−3.78 (m, 1H), 3.64−3.49 (m, 1H), 2.21−2.12 (m, 1H), 1.46 (dd, 3H, J_{PMe} = 17.0 Hz, J_{HMe} = 7.4 Hz), 1.42−1.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.7−127.0 (m, aromatic and alkene), 70.3, 49.0 (d, 1C, J = 2.4 Hz), 40.5 (d, 1C, J = 86.8 Hz), 24.3, 23.1 (d, 1C, J = 11.6 Hz), 14.0; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 41.4; IR ($CDCl_3$) 1197, 1110, 1060 cm^{-1}; LRMS (ESI) m/z 340 (M + H)$^+$.

(*E*)-Hepta-4,6-dien-1-ol (22). (*E*)-Hepta-4,6-dienoic acid ethyl ester (14.32 g, 92.9 mmol) was dissolved in anhydrous diethyl ether (750 mL) under a stream of argon and cooled to 0 °C in an ice bath. After stirring for 0.5 h, a solution of lithium aluminum hydride (1.80 g, 47.4 mmol) in anhydrous diethyl ether (200 mL) was added dropwise via a syringe pump over 45 min. The reaction was stirred at 0 °C until complete as determined by TLC. While maintaining the reaction at 0 °C a 5% sodium hydroxide solution was carefully added until the evolution of hydrogen gas ceased. During this period a white solid precipitated. The mixture was stirred an additional 20 min and the solid was vacuum filtered and washed with diethyl ether (3 × 150 mL). The filtrates were combined, concentrated in vacuo and purified by silica gel chromatography (3:1 pentane/EtOAc) to give **22** (8.96 g, 86%) as a colorless liquid: R_f 0.49 (3:1 pentane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.35−6.22 (m, 1H), 6.10−6.01 (m, 1H), 5.73−5.64 (m, 1H), 5.07 (d, 1H, J = 16.9 Hz), 4.95 (d, 1H, J = 10.2 Hz), 3.59 (m, 2H), 2.92 (br s, 1H) 2.15 (q, 2H, J = 7.5 Hz) 1.69−1.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5, 134.7, 131.8, 115.4, 62.4, 32.4, 29.1; IR ($CDCl_3$) 3622, 1006 cm^{-1}; LRMS (ESI) m/z 113 (M + H)$^+$.

Toluene-4-sulfonic Acid (*E*)-Hepta-4,6-dienyl Ester (23). *p*-Toluenesulfonyl chloride (18.18 g, 95.4 mmol) was added via a solid addition funnel to a cooled (0 °C, ice bath) solution of (*E*)-hepta-4,6-dien-1-ol (7.13 g, 63.6 mmol) and 1,4-diazabicylo[2.2.2]octane (14.26 g, 127 mmol) in anhydrous methylene chloride (75 mL). The reaction was slowly warmed to room temperature and stirred for 4 days during which time a white solid precipitated. The solid was filtered and washed with methylene chloride (3 × 25 mL). The filtrates were combined and concentrated in vacuo to afford an oil. The crude product was purified by flash chromatography (20:1 to 10:1 pentane/EtOAc) to yield **23** (11.73 g, 69%) as a clear viscous oil: R_f 0.58 (8:1 pentane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz)

δ 7.61 (d, 2H, J = 1.6 Hz), 7.58 (d, 2H, J = 1.6 Hz), 6.11−5.98 (m, 1H), 5.81−5.72 (m, 1H), 5.40−5.5.30 (m, 1H), 4.87 (d, 1H, J = 16.9 Hz), 4.78 (d, 1H, J = 10.1 Hz), 3.86−3.81 (m, 2H), 2.25 (s, 3H) 1.92 (q, 2H, J = 7.3 Hz) 1.59−1.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.1, 137.2, 133.5, 132.9, 132.7, 130.2, 128.3, 116.0, 70.1, 28.7, 28.5, 22.0; IR ($CDCl_3$) 1356, 1174, 1005, 962 cm^{-1}; LRMS (ESI) m/z 267 (M + Na)$^+$.

(*E*)-7-Bromo-hepta-1,3-diene (24). Toluene-4-sulfonic acid (*E*)-hepta-4,6-dienyl ester (8.00 g, 30.0 mmol) and anhydrous lithium bromide (7.83 g, 90.2 mmol) were refluxed in anhydrous acetone for 16 h. The reaction mixture was cooled to room temperature and concentrated in vacuo over a cool water bath. The resulting oil was dissolved in diethyl ether (100 mL), extracted with brine (3 × 100 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo over a cool water bath. The crude product, viscous amber oil **24** (5.04 g, 96%), was used without further purification: R_f 0.90 (8:1 pentane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.29−6.17 (m, 1H), 6.07−5.99 (m, 1H), 5.62−5.53 (m, 1H), 5.05 (d, 1H, J = 16.7 Hz), 4.92 (d, 1H, J = 10.0 Hz), 3.34 (t, 2H, J = 6.7 Hz), 2.17 (q, 2H, J = 7.1 Hz) 1.88 (quintet, 2H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 133.1, 132.7, 116.0, 33.5, 32.4, 31.2; LRMS (EI) m/z 176 (M + H)$^+$.

(*E*)-Hepta-4,6-dienyl(phenyl)phosphinic Acid Ethyl Ester (25). Diethyl phenylphosphonite (6.28 g, 31.7 mmol) was added dropwise to refluxing **24** (5.04 g, 28.8 mmol) under a constant stream of argon. The reaction was monitored by TLC and stopped after 5 h and allowed to cool to room temperature. The crude oil was purified by silica gel chromatography (EtOAc) to afford ester **25** (4.81 g, 63%) as an amber oil: R_f 0.46 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77−7.68 (m, 2H), 7.52−7.39 (m, 3H), 6.26−6.14 (m, 1H), 6.20 (dt, 1H, J = 16.9, 10.2 Hz), 5.93 (dd, 1H, J = 10.4, 10.4 Hz), 5.57−5.47 (m, 1H), 5.01 (d, 1H, J = 17.0 Hz), 4.90 (d, 1H, J = 10.3 Hz), 4.10−3.95 (m, 1H), 3.81−3.73 (m, 1H), 2.07 (q, 2H, J = 7.0 Hz), 1.90−1.52 (m, 4H), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3−128.7 (m, aromatic and alkene), 60.8 (d, 1C, J = 6.4 Hz), 33.6 (d, 1C, J = 16.2 Hz), 30.2, 28.8, 16.8 (d, 1C, J = 6.5 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 45.7; IR ($CDCl_3$) 1205, 1120, 1035 cm^{-1}; LRMS (ESI) m/z 265 (M + H)$^+$.

Hepta-4,6-dienyl(phenyl)phosphinic Acid (26). Hepta-4,6-dienyl(phenyl)phosphinic acid ethyl ester (3.74 g, 14.1 mmol) was refluxed in a solution of 2 N NaOH/EtOH (1:1, 250 mL) for 2.5 h. The reaction mixture was cooled and the ethanol was removed in vacuo. The remaining aqueous portion was acidified (pH = 3) with concentrated hydrochloric acid, extracted with methylene chloride (5 × 50 mL), dried over magnesium sulfate, and concentrated in vacuo to afford **26** (3.28 g, 98%) as a white solid: R_f 0.21 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.77 (br s, 1H), 7.68−7.61 (m, 2H), 7.43−7.32 (m, 3H), 6.23−6.10 (m, 1H), 5.91−5.83 (m, 1H), 5.49−5.39 (m, 1H), 4.98 (d, 1H, J = 16.9 Hz), 4.87 (d, 1H, J = 9.9 Hz), 1.96 (q, 2H, J = 6.7 Hz), 1.77−1.67 (m, 2H), 1.54−1.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.4−128.5 (m, aromatic and alkene), 115.6, 33.6 (d, 1C, J = 16.4 Hz), 30.9, 29.6, 21.7 (d, 1C, J = 3.2 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 45.9; IR ($CDCl_3$) 3305−2676 (br OH), 1717, 1174, 1004 cm^{-1}; LRMS (ESI) m/z 237 (M + H)$^+$.

Hepta-4,6-dienyl(phenyl)phosphinic Chloride (27). *N*,*N*-Diethyltrimethylsilylamine (0.400 g, 2.75 mmol) was added to a solution of anhydrous methylene chloride (6 mL) containing **26** (0.325 g, 1.38 mmol) and stirred at 0 °C for 2 h. The resulting solution was concentrated in vacuo, and the product was repeatedly dissolved in and concentrated from anhydrous benzene (4 × 15 mL) and placed on a vacuum line for 1 h. The residue was redissolved in anhydrous methylene chloride (8 mL) containing 2 drops of DMF and cooled to 0 °C and stirred for 0.5 h. Oxalyl chloride (0.198 mL, 2.27 mmol) was added dropwise over a 15 min period to the previous solution and stirred for 75 min. The reaction mixture was warmed to room temperature, stirred for an additional 45 min, and concentrated in vacuo, and the product was repeatedly dissolved in and concentrated from anhydrous benzene (4 × 15 mL) and placed on a vacuum line for 1 h. The resulting phosphinic chloride was used without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84−7.73 (m, 2H), 7.61−7.30 (m, 3H), 6.25−6.13 (m, 1H), 6.10−5.84 (m, 1H), 5.04−4.85 (m, 2H), 2.33−1.65 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.2−115.9 (m, aromatic and alkene), 36.5 (d, 1C, J = 81.0 Hz), 33.0 (d, 1C, J = 17.6 Hz), 21.9 (d, 1C, J = 4.2 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 58.0; IR ($CDCl_3$) 1665 cm^{-1}.

8-Phenyl-4a,5,6,7-tetrahydro-2*H*-1-oxa-8a-aza-8-phosphanaphthalene 8-Oxide (20). *N*,*O*-Bis(trimethylsilyl)hydroxylamine (0.305 g, 1.72 mmol) was added dropwise to a cooled (0 °C) solution of anhydrous methylene chloride (10 mL) containing **27** (0.350 g, 1.38 mmol) and stirred for 2 h. The resulting solution was concentrated in vacuo, and the product was repeatedly dissolved in and concentrated from anhydrous benzene (4 × 15 mL) and placed on a vacuum line for 1 h. The residue was dissolved in anhydrous methylene chloride (15 mL) and added dropwise to a solution of methylene chloride (10 mL) containing methanol (0.065 mL, 1.51 mmol) and tetra *n*-butylammonium periodate (0.656 g, 1.51 mmol) and stirred at 0 °C for 2 h. The reaction was warmed to room temperature and concentrated in vacuo. The crude product was purified by silica gel chromatography (20% methanol in EtOAc) to afford **20** as an amber oil: R_f 0.15 (20% methanol in EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83−7.76 (m, 2H), 7.48−7.36 (m, 3H), 5.82−5.77 (m, 1H), 5.63−5.57 (m, 1H), 4.65−4.59 (m, 1H), 4.17−4.07 (m, 1H), 4.06 (br s, 1H), 2.26−2.17 (m, 1H), 2.09−1.83 (m, 3H), 1.65−1.50 (m, 1H); ($CDCl_3$, 75 MHz) δ 132.3−125.9 (m, aromatic and alkene), 70.1 (d, 1C, J = 3.1 Hz), 59.1, 32.2 (d, 1C, J = 2.8 Hz), 28.1 (d, 1C, J = 81.1 Hz), 21.2 (d, 1C, J = 5.8 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 29.7; LRMS (ESI) m/z 250 (M + H)$^+$.

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Supporting Information Available: Proton, carbon, and phosphorus NMR spectra for new compounds and X-ray crystallographic data for **13** and **17a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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