P-Nitrosophosphate Compounds: New N−O Heterodienophiles and Nitroxyl Delivery Agents

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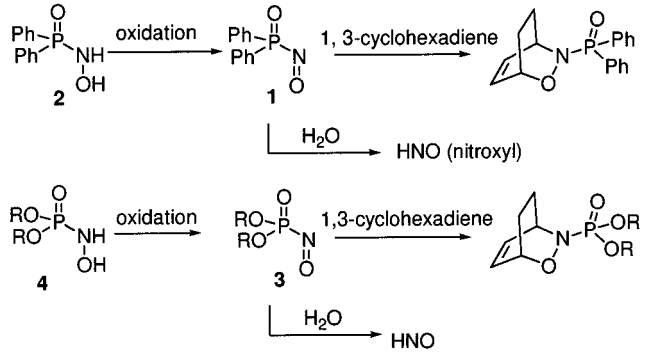
P-Nitrosophosphates, such as **9**, react as N−O heterodienophiles with 1,3-dienes to form highly functionalized cycloadducts that can be directly transformed into allylic phosphoramidates. The in situ periodate oxidation of the unstable *N*-hydroxyphosphoramidate precursors provides an efficient preparation of these new reactive intermediates. *P*-Nitrosophosphate (**9**) regioselectively reacts with 1-methoxy-1,3-butadiene to provide cycloadduct **16**. *P*-Nitrosophosphate (**9**) also reacts with 9,10-dimethylanthracene to give cycloadduct **17**, which undergoes retro Diels−Alder dissociation to reform **9**. In the absence of a 1,3-diene, the decomposition of **17** produces nitrous oxide, evidence for nitroxyl, the one-electron-reduced form of nitric oxide. An asymmetric *P*-nitrosophosphate reacted with 1,3-cyclohexadiene to form a mixture of diastereomeric cycloadducts (**19** and **20**) in a 1.6:1 ratio. These results identify *P*-nitrosophosphates as new species that react similarly to acyl nitroso compounds, making them useful synthetic intermediates and potential nitroxyl delivery agents.

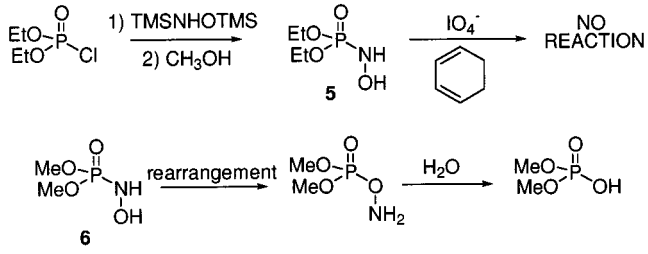
Introduction

P-Nitrosophosphine 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 unique phosphorus-containing cycloadducts (Scheme 1).[1] Reduction of the N−O bond of these compounds forms highly functionalized *cis*-1,4-phosphinamido allylic alcohols.[1] Such methodology should be applicable to the synthesis of a variety of new organophosphate and phosphoramidate derivatives via *P*-nitrosophosphate intermediates (**3**) produced from the oxidation of the corresponding *N*-hydroxyphosphoramidates (**4**, Scheme 1). *P*-Nitrosophosphine oxides (**1**) also hydrolyze to produce nitroxyl (HNO), the one-electron-reduced form of the biologically important signaling molecule nitric oxide (NO, Scheme 1).[1] We wish to report results regarding the preparation of *P*-nitrosophosphates (**3**) as new reactive intermediates that react with 1,3-dienes as N−O heterodienophiles and liberate nitroxyl upon reaction with nucleophiles.

Scheme 1



Scheme 2



Results and Discussion

Addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine to diethyl chlorophosphate followed by *O*-silyl group methanolysis produced a compound that displayed an NMR spectra consistent with that expected for diethyl *N*-hydroxyphosphoramidate (**5**, Scheme 2). Treatment of this material with tetra *N*-butylammonium periodate in the presence of 1,3-cyclohexadiene, however, did not produce the expected cycloadduct (Scheme 2). The failure to form the desired product in this reaction appears due to the general instability of *N*-hydroxyphosphoramidates. Recent work shows that dimethyl *N*-hydroxyphosphoramidate (**6**) quickly decomposes ($t_{1/2}$ = 15 min, room temperature) in water to the phosphoric acid by a PNHOH to $PONH_2$ rearrangement followed by hydrolysis (Scheme 2).[2] Such a rearrangement and subsequent reactions of **5** during *O*-silyl group methanolysis and isolation would explain the lack of cycloadduct formation upon the addition of oxidant and 1,3-diene.

These results forced the development of an alternative synthetic approach to *P*-nitrosophosphates. While dimethyl *N*-hydroxyphosphoramidate (**6**) decomposes by the pathway depicted in Scheme 2, the *O*-ethyl and benzyl derivatives of **6** are stable under the same condi-

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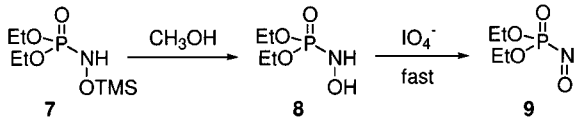
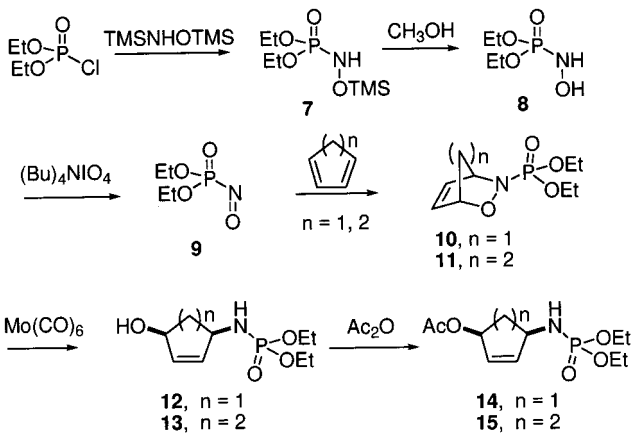
Scheme 3



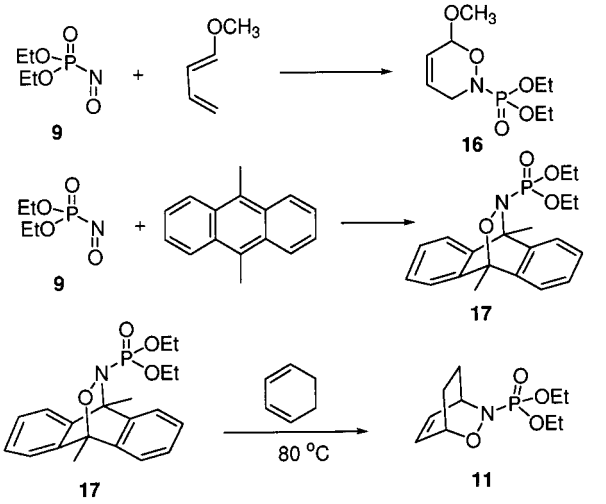
Scheme 4



tions.[2] Deprotection of an *O*-derivatized *N*-hydroxyphosphoramidate followed by oxidation at a faster rate than rearrangement provides, in principle, a method for generating the desired *P*-nitrosophosphates (Scheme 3). The rapid oxidation of hydroxamic acids and *N*-hydroxyphosphonamides by various periodates supports the feasibility of this approach.[1,3] The lability of the trimethyl silyl (TMS) group, removed by methanolysis,[4] directed our attention to *O*-TMS-protected diethyl *N*-hydroxyphosphoramidate (**7**) as a stable *p*-nitrosophosphate precursor (Scheme 3). If the periodate oxidation of diethyl *N*-hydroxyphosphoramidate (**8**) occurs faster than the PNHOH to $PONH_2$ rearrangement, then the addition of **7** to a methanol-containing solution of an organic periodate would be expected to produce the *P*-nitrosophosphate (**9**), which should react as an N−O heterodienophile (Scheme 3).

Treatment of diethyl chlorophosphate with *N*,*O*-bis(trimethylsilyl)hydroxylamine in anhydrous methylene chloride (CH_2Cl_2) produced a clear oil judged to be *O*-TMS diethyl *N*-hydroxyphosphoramidate (**7**) by proton NMR (Scheme 4). Addition of an anhydrous CH_2Cl_2 solution of **7** to a solution of tetra-*N*-butylammonium periodate, methanol, and either 1,3-cyclopentadiene or 1,3-cyclohexadiene in dry CH_2Cl_2 gratifyingly formed cycloadducts **10** and **11** in 67 and 70% yield, respectively (Scheme 4). These results indicate that methanolysis of **7** gives **8**, which undergoes oxidation faster than PNHOH to $PONH_2$ rearrangement to produce **9**, which reacts with 1,3-dienes as a heterodienophile (Scheme 4). The isolation and characterization of these cycloadducts (**10**, **11**) provides the first experimental evidence for the intermediacy of a *P*-nitrosophosphate (**9**). The yields of these conversions are based upon diethyl chlorophosphate and highlight the overall efficiency of four consecutive reactions: hydroxylamine addition, deprotection, oxidation, and cycloaddition (Scheme 4). Molybdenum hexacarbonyl N−O bond reduction afforded the corresponding *cis*-1,4-phosphoramidato allylic alcohols (**12** and **13**, 36 and 43% yield, respectively), which were further characterized by conversion to the acetates (**14** and **15**, 53 and 96% yield, respectively, Scheme 4).[1] While alcohols **12** and **13** appear well-situated for N to O migration of the phosphate group, the observation of a band at 1725 cm^{-1} in the infrared spectra of **14** and **15** supports the structural assignment of these esters and demonstrates a lack of phosphate group migration. This observed difference in the rate of phosphate group migration may be due to kinetic differences in the formation of the tetrahedral intermediates required for the N to O rearrangement of dimethyl *N*-hydroxyphosphoramidate (**6**, Scheme 2) and **12** and **13**. This sequence of reactions generates highly functionalized phosphoramidates in a direct and stereoselective manner.

Scheme 5



The *P*-nitrosophosphate (**9**), formed as described above, regioselectively reacted with 1-methoxy-1,3-butadiene to produce cycloadduct **16** in 76% yield (Scheme 5). Analysis of the ^{13}C NMR chemical shift of the methine carbon (δ = 98.7 ppm) established the structure of **16**.[1,5] The regiochemical outcome of this cycloaddition appears best rationalized by a steric argument and directly coincides with the previously observed regiochemistry in the reaction of a similar *P*-nitrosophosphine oxide and the same 1,3-diene.[1] Reaction of **9** with 9,10-dimethylanthracene produced cycloadduct **17** in 35% yield (Scheme 5). Heating **17** at 80 °C for 8 h in the presence of 1,3-cyclohexadiene produced **11** in 56% yield, demonstrating the ability of **17** to produce the *P*-nitrosophosphate (**9**) through a retro-Diels−Alder reaction similar to the acyl nitroso and *P*-nitrosophosphine oxide cycloadducts of this diene.[1,6] These results further extend the scope of these cycloadditions.

Experiments with an enantiopure asymmetric *P*-nitrosophosphate demonstrate the diastereoselective cycloaddition of these new intermediates. Treatment of commercially available (4*S*,5*S*)-2-chloro-4,5-dimethyl-1,3,2-dioxapholane 2-oxide (Anderson-Shapiro NMR Reagent)[7] with *N*,*O*-bis(trimethylsilyl)hydroxylamine in anhydrous CH_2Cl_2 produced the *O*-TMS-protected *N*-hydroxyphosphoramidate (**18**, Scheme 6). Addition of an

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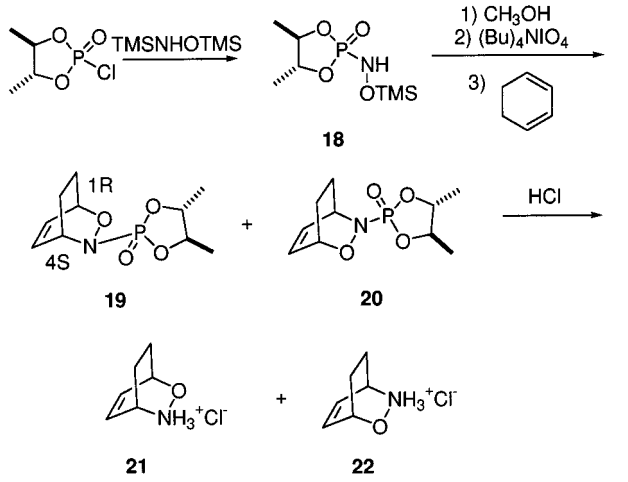
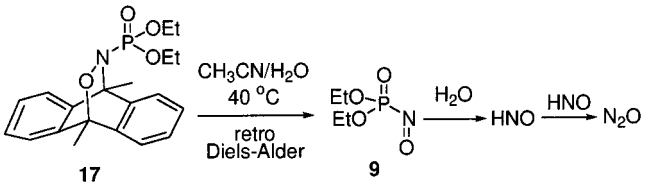
Scheme 6



Scheme 7



anhydrous CH_2Cl_2 solution of **18** to a solution of tetra-*N*-butylammonium periodate, methanol, and 1,3-cyclohexadiene gave the diastereomeric cycloadducts **19** and **20** (21% yield, 1.6:1 = **19**/**20**, Scheme 6). Phosphorus NMR experiments cleanly revealed the ratio of **19** to **20**. Acidic hydrolysis converted **19** and **20** into a mixture of the known enantiomeric oxazine hydrochloride salts **21** and **22**, and measurement of the optical rotation of this mixture provided information regarding the absolute stereochemistry of the major cycloadduct (**19**, Scheme 6).[8] A small but reproducible positive optical rotation for the mixture of **21** and **22** indicated that **21**, $[\alpha]_D = +24°$,[8] comprised the predominant enantiomer in the mixture. These measurements thus establish the absolute stereochemistry of the major cycloadduct (**19**) as (1*R*,4*S*), as depicted in Scheme 6. Despite this modest observed selectivity, these results demonstrate in principle the ability of asymmetric *p*-nitrosophosphates to undergo diastereoselective cycloadditions with 1,3-dienes. The accessibility of enantiopure 1,2-diols from processes such as the Sharpless asymmetric dihydroxylation[9] encourages the further development of *p*-nitrosophosphates as asymmetric N−O heterodienophiles for the preparation of a variety of enantiopure oxygen-, nitrogen-, and phosphorus-containing products.

Thermal decomposition of the *P*-nitrosophosphate and 9,10-dimethylanthracene cycloadduct (**17**) at 40 °C in a mixture of acetonitrile and water (1:1) produced nitrous oxide (46% yield, Scheme 7), as determined by gas chromatographic analysis of the reaction headspace. Detection of nitrous oxide, the dimerization and dehydration product of nitroxyl (HNO),[10] provides evidence for the formation of the biologically important one-electron-reduced form of nitric oxide during this reaction. These results, in addition to those presented in Scheme 5, suggest that in the absence of a 1,3-diene the retro-Diels−Alder dissociation of **22** produces the *P*-nitrosophosphate (**9**) that hydrolyzes to form HNO. Similar cycloadducts of acyl nitroso compounds also release nitroxyl through retro-Diels−Alder reactions in the absence of 1,3-dienes and the presence of nucleophiles.[11] Given the accumulating evidence of the biological importance of nitroxyl (vasorelaxant, inhibitor of thiol-containing enzymes, double-stranded DNA cleavage agent),[12] new compounds that donate nitroxyl will be of increasing interest and importance as pharmacological tools and therapeutic agents. These results identify *p*-nitrosophosphates as new species capable of nitroxyl release at biologically relevant temperatures and neutral pH in the absence of additional reagents.

In conclusion, *p*-nitrosophosphates represent new asymmetric N−O heterodienophiles that react with 1,3-dienes to produce complex oxygen-, nitrogen-, and phosphorus-containing cycloadducts and permit the direct introduction of the phosphoramidate functional group. In situ oxidation of the unstable *N*-hydroxyphosphoramidates provides an efficient method for the preparation of these reactive intermediates. An asymmetric *P*-nitrosophosphate reacted with 1,3-cyclohexadiene to form a diastereoselectively enriched mixture of cycloadducts, suggesting the further synthetic development of these species as asymmetric reagents. *P*-Nitrosophosphates also reacted with water to yield nitroxyl, the biologically important one-electron-reduced form of nitric oxide.

Experimental Section

General Considerations. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F-254 precoated plates obtained from E. Merck. Flash chromatography was performed on Mallinckrodt silica gel 60 (230−400 mesh). Proton NMR spectra were taken in commercial deuterated solvents on a Bruker Avance multinuclear spectrometer with all chemical shifts being reported in δ scale in parts per million from Me_4Si. Carbon-13 NMR spectra were taken on a Bruker Avance multinuclear spectrometer (75 MHz). Phosphorus-31 NMR spectra were taken on a Bruker Avance multinuclear spectrometer (121 MHz) and referenced to H_3PO_4 (defined as 0 ppm). Infrared spectra were obtained on a Perkin-Elmer 1600 Series FTIR spectrometer. Optical rotations were performed on a Rudolph Autopol IV polarimeter. Organic solvents were distilled from a drying agent prior to use. Commercially available reagents were used without further purification.

***N*-Diethylphosphoryl-*O*-(trimethylsilyl)hydroxylamine (7).** Diethyl chlorophosphate (0.300 g, 1.74 mmol) was added dropwise to a stirred solution of *N*,*O*-bis(trimethylsilyl)-hydroxylamine (0.370 g, 2.09 mmol) in anhydrous methylene chloride (10 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 0.5 h and concentrated in vacuo. The resulting white solid was stirred with anhydrous diethyl ether (10 mL), filtered to presumably remove insoluble

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phosphoric acid impurities, and concentrated in vacuo to afford **7** as a clear oil.

***N*-Diethylphosphoryl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (10).** *N*-Diethylphosphoryl-*O*-(trimethylsilyl)hydroxylamine (**7**, 0.420 g, 1.74 mmol) dissolved in anhydrous methylene chloride (10 mL) was added dropwise to a solution of 1,3-cyclopentadiene (0.230 g, 3.48 mmol), tetrabutylammonium periodate (0.754 g, 1.74 mmol), and anhydrous methanol (0.056 g, 1.74 mmol) dissolved in anhydrous methylene chloride (15 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for an additional 4 h. The crude product was purified by silica gel chromatography (2:1 EtOAc/pentane) to afford **10** (0.270 g, 67%) as a clear oil: R_f 0.24 (2:1 EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.46−6.44 (m, 1H), 6.28−6.25 (m, 1H), 5.17 (br s, 1H), 4.79 (br s, 1H), 4.18 (q, 2H, J = 7.2 Hz), 4.08 (q, 2H, J = 7.2 Hz), 2.00−1.96 (m, 2H), 1.73−1.69 (m, 2H), 1.36−1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.3 (d, 1C, J = 7.9 Hz), 132.7, 83.7, 64.5 (d, 1C, J = 7.3 Hz), 64.2 (d, 1C, J = 6.7 Hz), 63.9, 48.7 (d, 1C, J = 5.9 Hz), 16.5 (d, 1C, J = 2.1 Hz), 16.4 (d, 1C, J = 2.0 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 7.68; IR ($CDCl_3$) 1725, 1252, 1024 cm^{-1}; LRMS (FAB) m/z 256 $(M + Na)^+$. Anal. Calcd for $C_9H_{16}NO_4P$: C, 46.35; H, 6.92; N, 6.01. Found: C, 46.12; H, 7.03; N, 5.41.

***N*-Diethylphosphoryl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (11).** *N*-Diethylphosphoryl-*O*-(trimethylsilyl)hydroxylamine (**7**, 0.420 g, 1.74 mmol) dissolved in anhydrous methylene chloride (10 mL) was added dropwise to a solution of 1,3-cyclohexadiene (0.279 g, 3.48 mmol), tetrabutylammonium periodate (0.754 g, 1.74 mmol), and anhydrous methanol (0.056 g, 1.74 mmol) dissolved in anhydrous methylene chloride (15 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for an additional 4 h. The crude product was purified by silica gel chromatography (2:1 EtOAc/pentane) to afford **11** (0.300 g, 70%) as a clear oil: R_f 0.35 (2:1 EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.51−6.45 (m, 1H), 6.39−6.34 (m, 1H), 4.47−4.44 (m, 1H), 4.19−4.16 (m, 1H), 4.08−3.91 (m, 4H), 2.10−2.01 (m, 2H), 1.33−1.26 (m, 2H), 1.23−1.13 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.5 (d, 1C, J = 3.6 MHz), 131.1, 70.0, 64.2 (d, 1C, J = 7.0 Hz), 63.8 (d, 1C, J = 6.4 Hz), 49.0, 23.8, 22.7 (d, 1C, J = 11.7 Hz), 16.5 (d, 1C, J = 4.9 Hz), 16.4 (d, 1C, J = 6.1 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 6.22; IR ($CDCl_3$) 1716, 1252, 1041 cm^{-1}; LRMS (FAB) m/z 270 $(M + Na)^+$. Anal. Calcd for $C_{10}H_{18}NO_4P$: C, 48.58; H, 7.34; N, 5.67. Found: C, 47.47; H, 7.38; N, 5.35.

***N*-Diethylphosphoryl-*cis*-4-amino-2-cyclopenten-1-ol (12).** Molybdenum hexacarbonyl (0.248 g, 0.940 mmol) was added to a solution of **10** (0.219 g, 0.940 mmol) in (15:1 acetonitrile/H_2O, 15 mL). The mixture was refluxed for 4 h, concentrated in vacuo, and partitioned between 1:1 EtOAc/1 N citric acid (15 mL). Sodium periodate was added to the aqueous layer until it became clear, and the aqueous layer was extracted with EtOAc (5 × 10 mL). The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give a colorless oil. The crude oil was purified by flash chromatography (EtOAc to 10% MeOH in EtOAc) to afford **12** (0.080 g, 36%) as a clear oil: R_f 0.19 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92−5.90 (m, 1H), 5.82−5.80 (m, 1H), 4.56−4.53 (m, 1H), 4.30−4.26 (m, 1H), 4.05−3.93 (m, 5H), 2.66−2.56 (m, 1H), 1.59−1.54 (m, 1H), 1.30 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9, 135.5 (d, 1C, J = 5.3 Hz), 75.3, 62.7 (d, 1C, J = 2.5 Hz), 55.8, 43.1 (d, 1C, J = 4.0 Hz), 16.5 (d, 1C, J = 6.9 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 8.96; IR ($CDCl_3$) 3404, 3243, 1725, 1218, 1023, cm^{-1}; LRMS (FAB) m/z 258 $(M + Na)^+$. Anal. Calcd for $C_9H_{18}NO_4P$: C, 45.96; H, 7.71; N, 5.95. Found: C, 47.81; H, 7.79; N, 5.22. Acetic anhydride (0.073 g, 0.714 mmol) was added to a solution of **12** (0.084 g, 0.357 mmol) in 2:1 pyridine/water (10 mL) and stirred at 23 °C for 48 h. The mixture was repeatedly diluted with EtOAc (5 × 10 mL) and concentrated in vacuo to remove traces of pyridine. The resulting oil was extracted with EtOAc (5 × 10 mL), washed with brine, and dried over magnesium sulfate. The crude product was purified by flash chromatography (EtOAc) to afford the acetate **14** (0.053 g, 53%) as a colorless oil: R_f 0.47 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.95−5.93 (m, 1H), 5.86−5.84 (m, 1H), 5.43 (br s, 1H), 4.04−4.00 (m, 5H), 2.79−2.69 (m, 1H), 2.63 (br s, 1H), 1.98 (s, 3H), 1.53−1.46 (m, 1H), (t, 6H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 138.6 (d, 1C, J = 5.5 Hz), 131.9, 77.9, 62.8 (d, 1C, J = 4.7 Hz), 55.9, 40.6 (d, 1C, J = 3.6 Hz), 21.5, 16.6 (d, 1C, J = 6.3 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 8.54; IR ($CDCl_3$) 3404, 1725, 1243, 1041 cm^{-1}; LRMS (FAB) m/z 278 $(M + H)^+$. Anal. Calcd for $C_{11}H_{20}NO_5P$: C, 47.65; H, 7.27; N, 5.05. Found: C, 50.20; H, 7.67; N, 4.39.

***N*-Diethylphosphoryl-*cis*-4-amino-2-cyclohexen-1-ol (13).** Molybdenum hexacarbonyl (0.233 g, 0.884 mmol) was added to a solution of **11** (0.218 g, 0.884 mmol) in 15:1 acetonitrile/H_2O (15 mL). The mixture was refluxed for 4 h, concentrated in vacuo, and partitioned between 1:1 EtOAc/1 N citric acid (15 mL). Sodium periodate was added to the aqueous layer until it became clear, and the aqueous layer was extracted with EtOAc (5 × 10 mL). The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give an oil. The crude oil was purified by flash chromatography (EtOAc to 10% MeOH in EtOAc) to afford **13** (0.089 g, 41%) as a clear oil: R_f 0.20 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.86−5.75 (m, 2H), 4.13−4.02 (m, 5H), 3.60 (br s, 1H), 3.01 (br s, 1H), 1.87−1.68 (m, 4H), 1.35−1.31 (t, 6H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.7, 132.6 (d, 1C, J = 24.7 Hz), 64.4, 62.7 (d, 1C, J = 5.0 Hz), 47.2, 29.1, 28.0 (d, 1C, J = 3.6 Hz), 16.5 (d, 1C, J = 6.9 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 9.58; IR ($CDCl_3$) 3409, 3284, 1724, 1232, 1048 cm^{-1}; LRMS (FAB) m/z 272 $(M + Na)^+$. Anal. Calcd for $C_{10}H_{20}NO_4P$: C, 48.19; H, 8.09; N, 5.62. Found: C, 48.66; H, 7.96; N, 4.92. Acetic anhydride (0.052 g, 0.514 mmol) was added to a solution of **13** (0.064 g, 0.257 mmol) in 2:1 pyridine/water (10 mL) and stirred at 23 °C for 48 h. The mixture was repeatedly diluted with EtOAc (5 × 10 mL) and concentrated in vacuo to remove traces of pyridine. The resulting oil was extracted with EtOAc (5 × 10 mL), washed with brine, and dried over magnesium sulfate. The crude product was purified by flash chromatography (EtOAc) to afford the acetate **15** (0.072 g, 96%) as a colorless oil: R_f 0.44 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56−5.81 (m, 1H), 5.73−5.69 (m, 1H), 5.10 (q, 1H, J = 4.0 Hz), 4.03−3.99 (m, 4H), 3.59 (br s, 1H), 2.56 (br s, 1H), 1.98 (s, 3H), 1.98−1.54 (m, 4H), 1.27 (t, 6H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 135.7 (d, 1C, J = 5.6 Hz), 127.6, 66.7, 62.7 (d, 1C, J = 4.6 Hz), 47.5, 28.1 (d, 1C, J = 3.7 Hz), 26.3, 21.6, 16.6 (d, 1C, J = 6.6 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 9.23; IR ($CDCl_3$) 3412, 1725, 1243, 1032 cm^{-1}; LRMS (FAB) m/z 292 $(M + H)^+$. Anal. Calcd for $C_{12}H_{22}NO_4P$: C, 49.48; H, 7.61; N, 4.81. Found: C, 50.78; H, 7.79; N, 4.52.

Diethyl *P*-Nitrosophosphate-1-methoxy-1,3-butadiene Cycloadduct (16). *N*-Diethylphosphoryl-*O*-(trimethylsilyl)-hydroxylamine (**7**, 0.420 g, 1.74 mmol) dissolved in anhydrous methylene chloride (10 mL) was added dropwise to a solution of 1-methoxy-1,3-butadiene (0.293 g, 3.48 mmol), tetrabutylammonium periodate (0.754 g, 1.74 mmol), and anhydrous methanol (0.056 g, 1.74 mmol) dissolved in anhydrous methylene chloride (15 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for an additional 4 h. The crude product was purified by silica gel chromatography (2:1 EtOAc/pentane) to afford **16** (0.330 g, 76%) as a clear oil: R_f 0.31 (2:1 EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.12−6.09 (m, 1H), 5.81−5.75 (m, 1H), 4.91 (br s, 1H), 4.25−4.11 (m, 4H), 3.83 (br s, 1H), 3.52 (s, 3H), 1.36 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 128.2 (d, 1C, J = 10.6 Hz), 124.0, 98.7 (d, 1C, J = 3.6 Hz), 64.1 (d, 1C, J = 6.2 Hz), 63.6 (d, 1C, J = 5.4 Hz), 56.4, 45.3 (d, 1C, J = 3.5 Hz), 16.5 (d, 1C, J = 6.3 Hz), 16.3 (d, 1C, J = 6.4 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 5.57; IR ($CDCl_3$) 1724, 1248, 1056 cm^{-1}; LRMS (FAB) m/z 274 $(M + Na)^+$. Anal. Calcd for $C_{20}H_{24}NO_4P$: C, 43.03; H, 7.22; N, 5.58. Found: C, 42.47; H, 7.25; N, 4.10.

Diethyl *p*-Nitrosophosphate-9,10-dimethylanthracene Cycloadduct (17). *N*-Diethylphosphoryl-*O*-(trimethylsilyl)-hydroxylamine (**7**, 0.420 g, 1.74 mmol) dissolved in anhydrous methylene chloride (10 mL) was added dropwise to a solution

of 9,10-dimethylanthracene (0.718 g, 3.48 mmol), tetrabutylammonium periodate (0.754 g, 1.74 mmol), and anhydrous methanol (0.056 g, 1.74 mmol) dissolved in anhydrous methylene chloride (15 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for an additional 4 h. The crude product was purified by silica gel chromatography (2:1 pentane/EtOAc) to afford **17** (0.230 g, 36%) as a clear oil: R_f 0.25 (2:1 pentane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.14 (m, 8H), 3.82−3.74 (m, 2H), 3.64−3.56 (m, 2H), 2.35 (s, 3H), 2.11 (s, 3H), 0.97 (t, 6H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.3, 142.1, 142.0, 127.6, 127.3, 121.2, 120.8, 78.3, 63.9 (d, 1C, J = 6.8 Hz), 61.1, 16.4 (d, 1C, J = 6.9 Hz), 16.1, 15.5; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 5.36; IR ($CDCl_3$) 1724, 1248, 1030 cm^{-1}; LRMS (FAB) *m*/*z* 374 (M + H)$^+$. Anal. Calcd for $C_{20}H_{24}NO_4P$: C, 64.33; H, 6.48; N, 3.77. Found: C, 64.08; H, 6.44; N, 3.59.

Retro-Diels−Alder Dissociation of 17. A solution of **17** (0.108 g, 0.289 mmol) and 1,3-cyclohexadiene (0.046 g, 0.577 mmol) in anhydrous toluene (2.0 mL) was heated in a sealed reaction tube under an argon atmosphere at 80 °C for 8 h. After cooling to 23 °C, the reaction mixture was concentrated in vacuo to give an oil that was purified by flash chromatography (2:1, pentane/EtOAc) to afford **11** (0.040 g, 56%).

***N*-(4*S*,5*S*)-4,5-Dimethyl-1,3,2-dioxaphospholanoyl-*O*-(trimethylsilyl)hydroxylamine (18).** (4*S*,5*S*)-2-Chloro-4,5-dimethyl-1,3,2-dioxaphospholane 2-oxide (0.500 g, 2.93 mmol) was added dropwise to a stirred solution of *N*,*O*-bis(trimethylsilyl)hydroxylamine (0.624 g, 3.52 mmol) in anhydrous methylene chloride (10 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 0.5 h and concentrated in vacuo. The resulting white solid was stirred with anhydrous diethyl ether (10 mL), filtered, and concentrated in vacuo to afford **18** as a clear oil.

***N*-(4*S*,5*S*)-4,5-Dimethyl-1,3,2-dioxaphospholanoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (19, 20).** A solution of **18** (0.695 g, 2.93 mmol) in anhydrous methylene chloride (10 mL) was added dropwise to a solution of 1,3-cyclohexadiene (0.470 g, 5.86 mmol), tetrabutylammonium periodate (1.40 g, 3.23 mmol), and anhydrous methanol (0.131 g, 3.23 mmol) dissolved in anhydrous methylene chloride (15 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for an additional 4 h. The crude product was purified by silica gel chromatography (2:1 EtOAc/pentane) to afford a mixture of **19** and **20** (0.149 g, 21%) as a clear oil: R_f 0.38 (2:1 EtOAc/pentane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.73−6.61 (m, 2H), 6.54−6.46 (m, 2H), 4.65−4.63 (m, 2H), 4.44−4.42 (m, 2H), 4.36−4.20 (m, 4H), 2.31−2.14 (m, 4H), 1.45−1.32 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.3, 132.2, 131.0, 130.9, 83.1, 82.4, 81.7, 81.5, 70.6, 49.7, 49.6, 24.1, 24.0, 22.5, 22.3, 18.7, 18.6, 18.2, 18.1; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 23.7, 23.6 (1.6:1 ratio); IR ($CDCl_3$) 1724, 1267, 1045 cm^{-1}; LRMS (FAB) *m*/*z* 268 (M + Na)$^+$. Anal. Calcd for $C_{10}H_{16}NO_4P$: C, 48.98; H, 6.58; N, 5.71. Found: C, 48.87; H, 6.99; N, 4.40.

2-Oxa-3-azabicyclo[2.2.2]oct-5-ene Hydrochloride Salt (21, 22). A solution of **19** and **20** (0.0885 g, 0.348 mmol) in 6 M HCl (5 mL) was stirred at room temperature for 4 days. The reaction mixture was purified on a Dowex 50 × 2−400 ion-exchange resin column eluted first with water (100 mL) followed by 0.3 M HCl (40 mL). Concentration of the acid wash fractions gave **21** and **22** (0.040 g, 78%) as a white solid: $[\alpha]^{20}_D$ +2.5 (*c* 1.36, MeOH); ^{1}H NMR (D_2O, 300 MHz) δ 6.82−6.77 (m, 1H), 6.54−6.49 (m, 1H), 4.92−4.89 (m, 1H), 4.51−4.49 (m, 1H), 2.23−1.97 (m, 2H), 1.57−1.42 (m, 2H).

Identification of Nitrous Oxide from the Retro-Diels−Alder Dissociation of 17. A solution of **17** (0.037 g, 0.100 mmol) in acetonitrile (1.0 mL) and water (1.0 mL) was heated at 40 °C in a 25 mL round-bottom flask equipped with a rubber septum and a stirring bar. After 12 h, 250 μL of the reaction headspace was removed and injected onto a 6890 Hewlett-Packard gas chromatograph equipped with a thermal conductivity detector, a 6 ft × 1/8 in. Porapak Q column at an operating oven temperature of 50 °C (injector and detector 100 °C) with a flow rate of 16.67 mL/min (He, carrier gas). The retention time of nitrous oxide was 2.61 min and identical to a known sample of N_2O (Aldrich). The yield of nitrous oxide was calculated on the basis of a standard curve generated by injecting known amounts of nitrous oxide.

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Supporting Information Available: Proton and carbon NMR spectra are provided for compounds **10**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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