N-Phosphinoylnitroso Compounds: New Asymmetric N−O Heterodienophiles and Nitroxyl Delivery Agents

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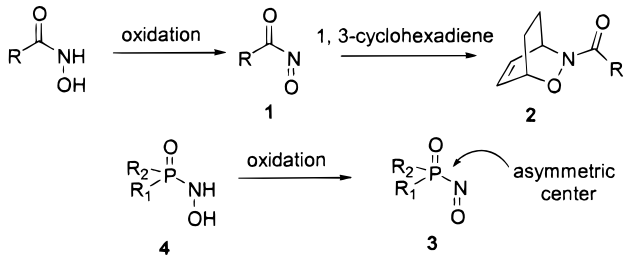
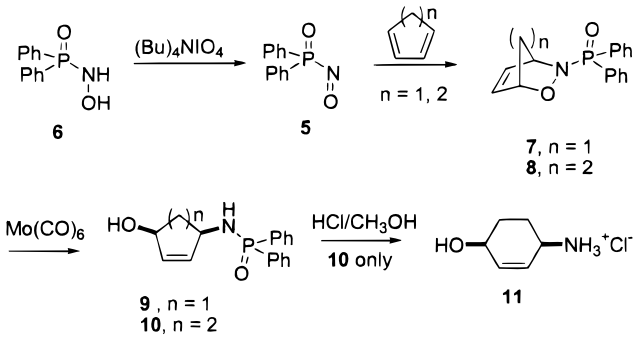
Nitroso compounds occupy a prominent position in organic chemistry as both useful synthetic intermediates and molecules of biological interest.[1] Acyl nitroso compounds (**1**) react with conjugated 1,3-dienes as N−O heterodienophiles to produce *N*-acyl-3,6-dihydro-1,2-oxazines (**2**), highly functionalized cycloadducts that represent the starting point for the asymmetric synthesis of many nitrogen-containing compounds (Scheme 1).[2] Interest in the diverse interactions of nitric oxide (NO) with various biological systems has led to the identification, synthesis, and characterization of new NO donor molecules, including many nitroso-containing compounds.[3] We wish to report the formation of *N*-phosphinoylnitroso compounds (**3**), new asymmetric (when $R_1 \neq R_2$) reactive intermediates, which diastereoselectively react with 1,3-dienes as N−O heterodienophiles. This reactivity allows the direct and stereoselective introduction of the Lewis basic phosphinamide functional group present in a number of asymmetric catalysts.[4] In addition to the potential synthetic utility of these molecules, *N*-phosphinoylnitroso compounds (**3**), produced by the oxidation of N-phosphinoylhydroxylamines (**4**, Scheme 1), hydrolyze to liberate nitroxyl (HNO), the biologically important reduced form of nitric oxide.[5]

Scheme 1



Scheme 2



The intermediacy of *N*-phosphinoylnitroso compound (**5**) is indicated from trapping experiments with 1,3-dienes (Scheme 2). Periodate oxidation of *N*−(diphenylphosphinoyl)hydroxylamine (**6**),[6] in the presence of 1,3-cyclopentadiene or 1,3-cyclohexadiene produced cycloadducts **7** and **8** in 80 and 88% yield, respectively (Scheme 2). Molybdenum hexacarbonyl N−O bond reduction afforded the corresponding alcohols (**9** and **10**, 53 and 78% yield, respectively) that were further characterized by acetylation (Scheme 2).[7] This sequence of reactions provides a direct and stereoselective method for the introduction of the phosphinamide functional group into the variety of compounds accessible through Scheme 1. Acid methanolysis of (**10**) removed the phosphinamide group affording the hydrochloride salt of the amino alcohol (**11**) in 49% yield (Scheme 2).

Table 1 summarizes the products and yields of the reactions of *N*-phosphinoylnitroso compound (**5**) with acyclic (entries 1−6), electron-rich (entries 1, 3, 4, and 6), electron-poor (entry 5), and aromatic (entry 7) 1,3-dienes. Compound **5**, formed by the periodate oxidation of **6**, regioselectively reacted with unsymmetric 1,3-dienes to produce the corresponding cycloadducts (entries 3−6). The structure of the major regioisomer (**14**) from the reaction of **5** with *trans*-piperylene was determined by ^{13}C NMR chemical shift analysis of the methine carbon.[8] The structures of **16** and **18** were determined by ^{13}C NMR chemical shift analysis, and the structure of **17** was determined by single-crystal X-ray crystallography.[9] The observed regiochemistry for entries 4−6 is consistent with that expected on the basis of previous results from cycloadditions between acyl nitroso compounds and similar 1,3-dienes and on the basis of theoretical arguments.[10,11] Heating **19** overnight at 80 °C in the presence of 1,3-cyclohexadiene produced **8** in 52% yield demonstrating the ability of **19** to produce **5** non-oxidatively through a retro-Diels Alder reaction similar to acyl nitroso cycloadducts of this diene.[2c,12]

Experiments with a racemic asymmetric *N*-phosphinoylnitroso compound demonstrate the diastereoselective cycloaddition of these reactive intermediates. Periodate oxidation of *N*-(benzylphenylphosphinoyl)hydroxylamine (**20**), in the presence of 1,3-cyclopentadiene or 1,3-cyclohexadiene produced chromatographically separable mixtures of the diastereomeric cycloadducts **22a**,**b** (85% yield, 35:1 = **22a**/**22b**, Scheme 3) and **23a**,**b** (87% yield, 21:1 = **23a**/**23b**, Scheme 3). The relative stereochemistry of the major cycloadducts (**22a** and **23a**) was determined by single-crystal X-ray crystallography.[13] While a clear mechanistic ex-

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(9) Crystal data for **17**, $C_{20}H_{22}NO_4P$, monoclinic at 293 K, $P2_1-C^2_2$ (No. 4), colorless crystal, $a = 10.255(1)$ Å, $b = 7.1019(9)$ Å, $c = 13.085(2)$ Å, $\beta = 115.035(5)°$, $Z = 2$, R1 = 0.054, wR2 = 0.0098, GOF = 1.016.

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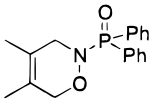
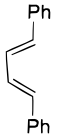
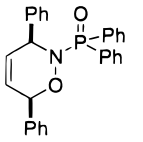
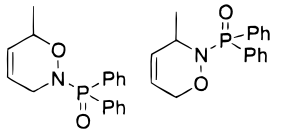
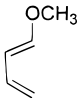
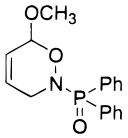
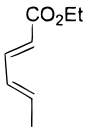
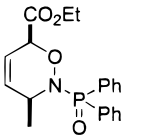
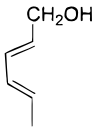
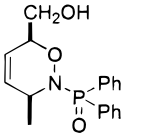
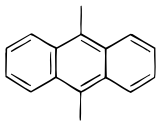
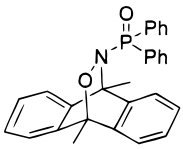
Table 1. Reactions of **5** with Various 1,3-Dienes

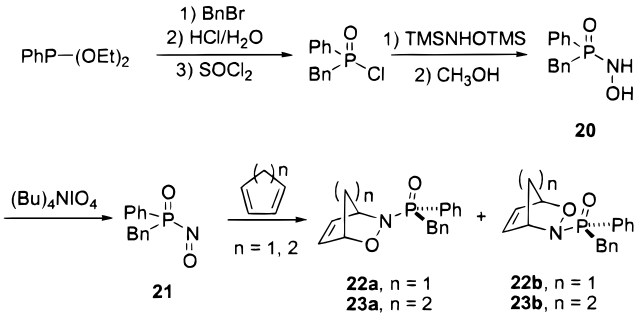
Entry	1, 3-Diene	Product	Yield
1			**12**, 49%
2			**13**, 34%
3			**14**:**15**, 2.5:1 82%
4			**16**, 80%
5			**17**, 42%
6			**18**, 81%
7			**19**, 73%

planation of the high levels of diastereoselectivity observed with the structurally simple phosphinoylnitroso compound (**21)** remains uncertain, the direct attachment of the asymmetric center to the reactive nitroso group of **21** would be expected to enhance the diastereoselectivity. Analytical chiral HPLC resolution of the enantiomers of **20** clearly demonstrates the feasibility for the formation of enantiomerically enriched cycloadducts from this reaction.

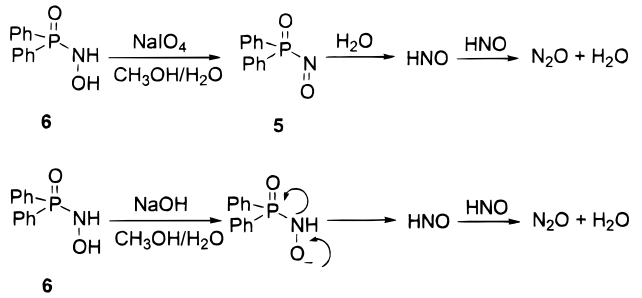
Finally, oxidative activation or basic decomposition of *N*-phosphinoylhydroxylamines affords nitroxyl (HNO), the one-electron reduced form of nitric oxide (NO). Gas chromatographic headspace analysis after periodate oxidation of **6** or **20** in the absence of a conjugated 1,3-diene in 1:1 CH_3OH:H_2O produced nitrous oxide (35 and 49% yield, respectively; Scheme 4). Identification of nitrous oxide, the stable dimerization and

(13) Crystal data for **22a**, $C_{18}H_{18}NO_2P$, monoclinic at 293 K, $P2_1/n$ (an alternate setting of $P2_1/c-C^5_{2h}$ [No. 14]), colorless crystal, a = 16.931(1) Å, b = 5.7138(3) Å, c = 17.551(1) Å, β = 113.559(5)°, Z = 4, R1 = 0.105, wR2 = 0.156, GOF = 1.099. Crystal data for **23a**, $C_{19}H_{20}NO_4P$, monoclinic at 293 K, $P2_1/n$ (an alternate setting of $P2_1/c-C^5_{2h}$ [No. 14]), colorless crystal, a = 17.092(2) Å, b = 5.927(1) Å, c = 17.851(2) Å, β = 112.576(8)°, Z = 4, R1 = 0.161, wR2 = 0.114, GOF = 0.997.

Scheme 3



Scheme 4



dehydration product of nitroxyl, provides strong evidence for the intermediacy of nitroxyl.[14] As with acyl nitroso compounds, the direct hydrolysis of an *N*-phosphinoylnitroso compound would produce nitroxyl and ultimately nitrous oxide.[15] *N*−(Diphenylphosphinoyl)hydroxylamine (**6**) also represents a phosphorus analogue of Piloty's acid (*N*-hydroxybenzenesulfonamide), a compound known to liberate nitroxyl under basic conditions.[16] Treatment of **6** with sodium hydroxide (10 equiv) in a water/methanol solution produced nitrous oxide (20% yield) indicative of nitroxyl formation presumably through base-catalyzed disproportionation similar to Piloty's acid (Scheme 4).[16]

In summary, *N*-phosphinoylnitroso compounds represent exciting new intermediates possessing divergent reactivity. The presented results allow them to be considered as new asymmetric N−O heterodienophiles that permit the direct diastereoselective introduction of the phosphinamide functional group, or as a new group of nitroxyl delivery agents.

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Supporting Information Available: Full experimental details including the synthesis and characterization of all compounds including the X-ray crystallographic data of **17**, **22a**, and **23a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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