Endocyclic Restriction Test: Applications to Transfers of Oxygen from Nitrogen and from Sulfur to Phosphorus(III)

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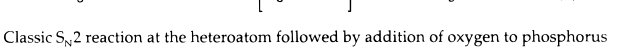
Abstract: The geometries allowed for formal transfers of oxygen to the phosphorus(III) of a phosphine from a nitrone, an *O*-acetylhydroxylamine, and a sulfoxide have been evaluated by the endocyclic restriction test. Investigations of the conversions of **1** to **2**, **16** to **17**, and **28** to **29**, by isotopic labeling, substituent effect, and kinetic and spectroscopic experiments, reveal the operation of different mechanisms for each of these transfers. For **1**, oxygen addition to phosphorus is the preferred mechanism. In the case of **16**, the mechanism involves nucleophilic displacement of oxygen from nitrogen by phosphorus to give **26** followed by oxygen addition to phosphorus. In acetic acid, the oxygen is added to **26** from water in the workup whereas in toluene the oxygen is provided by the acetate produced by the displacement. For **28,** either addition by oxygen of the sulfoxide to activated phosphorus or addition by phosphorus to sulfur of the sulfoxide precedes oxygen transfer.

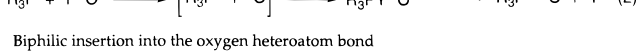
Reactions involving transfers of oxygen from heteroatoms to phosphorus(III) giving the deoxygenated heteroatom and the corresponding phosphine oxides are well-known processes.[1] A number of different mechanisms have been suggested for these oxidations. The present work evaluates the geometries allowed for transfers of oxygen from a nitrone, an *O*-acetylhydroxylamine, and a sulfoxide to phosphorus(III) by use of the endocyclic restriction test in order to distinguish between the alternative possible mechanisms.[2]

The possible mechanisms for reactions of heteroatom−oxygen single bonds with the phosphorus(III) of a phosphine are shown in generalized form in eqs 1−5.[4−13] The mechanisms are (1) classic S_N2 substitution at oxygen,[3] (2) classic S_N2 substitution at the heteroatom followed by addition of oxygen to phosphorus, (3) biphilic insertion into the oxygen heteroatom bond, (4) a radical reaction, and (5) initial bonding between oxygen and phosphorus in an addition−elimination sequence. Mechanisms 3−5 are also applicable to an oxygen formally multiply bonded to a heteroatom. For multiply bonded systems two other possibilities, (6) addition to the heteroatom or (7) addition to the adjacent atom, are plausible mechanisms.

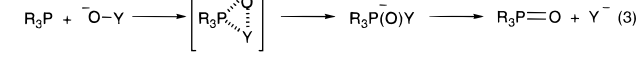
Classic S_N2 reaction at oxygen



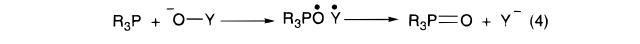
Classic S_N2 reaction at the heteroatom followed by addition of oxygen to phosphorus



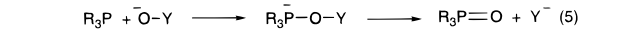
Biphilic insertion into the oxygen heteroatom bond



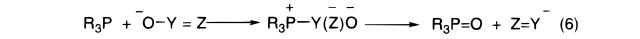
Radical reaction



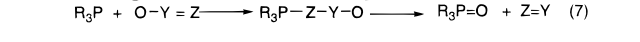
Addition elimination



Addition to Y



Addition to Z



Mechanistic investigations of the reactions of phosphorus(III) with nitrones and with *O*-acylhydroxylamines have been reported.[4] Hasimoto et al. have proposed deoxygenation of nitrones by triethyl phosphite occurs by initial addition of phosphorus to nitrogen followed by formation of an oxygen phosphorus bond and cleavage of the nitrogen phosphorus bond to produce trimethyl phosphate (eq 6).[5] Milliet and Lusinchi have proposed initial addition of trimethyl phosphite to the iminyl carbon of the nitrone followed by loss of a methyl group from a phosphite oxygen, bonding of the oxygen to phosphorus, and elimination of dimethyl phosphate to give the imine (eq 7).[6] The reaction of triphenyl phosphine and *N*,*O*-dibenzoylhydroxylamine has been shown by Wasserman and Koch to

[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1996.

(1) (a) Kirby, A. J.; Warren, S. G. *The Organic Chemistry of Phosphorus*; Elsevier: New York, 1967. (b) Emsley, J.; Hall, D. *The Chemistry of Phosphorus*; John Wiley and Sons: New York, 1976. (c) Smith, D. J. H. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, England, 1979; pp 1127−1188. (d) Rowley, A. G. In *Organophosphorus Reagents in Synthesis*; Cadogan, J. I. G., Ed.; Academic: New York, 1979; pp 295−350.

(2) Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215. We note that endocyclic restriction provides only a permissive test of reaction geometry (vide infra).

(3) While a literal definition of an S_N2 reaction denotes a second-order nucleophilic substitution at carbon, we believe the experimental and theoretical precedents are sufficient to use the term classic S_N2 to denote nucleophilic substitution which proceeds at any atom through a trigonal bipyramidal transition state with the ending and leaving groups in the apical positions.

(4) For the first report of deoxygenation of a nitrone by a phosphine, see: Horner, L.; Hoffmann, H. *Angew. Chem.* **1956**, *68*, 473.

(5) (a) Hashimoto, S.; Furukawa, I.; Fujimoto, S. *Nippon Kagaku Kaishi* **1972**, 391; *Chem. Abstr.* **1972**, *76*, 112403. (b) Hashimoto, S.; Furukawa, I.; Katami, T. *Nippon Kagaku Kaishi* **1974**, 511; *Chem. Abstr.* **1974**, *80*, 145023.

(6) Milliet, P.; Lusinchi, X. *Tetrahedron* **1979**, *35*, 43.

(7) Wasserman, H. H.; Koch, R. C. *Chem. Ind.* **1956**, 1014.

(8) Stec, W.; Okruszek, A.; Michalski, J. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1973**, *21*, 445.

(9) Emerson, T. R.; Rees, C. W. *J. Chem. Soc.* **1964**, 2319. Ramirez, F.; Aguiar, A. M. *Abstracts of Papers,* 134th Meeting of the American Chemical Society; American Chemical Society: Washington, DC, 1958; 42N.

(10) Amonoo-Neizer, A. H.; Ray, S. K.; Shaw, R. A.; Smith, B. C. *J. Chem. Soc.* **1965**, 4296.

(11) Luckenbach, R.; Herweg, G. *Liebigs Ann. Chem.* **1976**, 2305.

(12) Szmant, H. H.; Cox, O. *J. Org. Chem.* **1966**, *31*, 1595.

(13) Olah, G. A.; Gupta, B. G. B.; Narang, S. C. *Synthesis* **1978**, 137.

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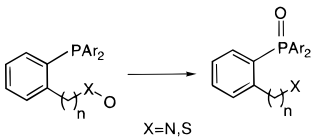
proceed by displacement at nitrogen by phosphorus to give a stable phosphorus ylide (eq 2).[7] In the transfer of oxygen from an amine oxide to phorphorus(III), Stec observed a high degree of retention at phosphorus and proposed an addition−elimination sequence (eq 5).[8] Similar pathways have been suggested by Rees, Ramirez, and Milliet.[6,9]

Three different mechanisms involving valence expansion at phosphorus followed by loss of the phosphine oxide have been proposed for the transfer of oxygen from the sulfur of a sulfoxide to phosphorus(III) by Amonoo-Neizer et al.[10] These mechanisms include initial nucleophilic attack of oxygen at phosphorus to give a valence-expanded intermediate (eq 5), initial nucleophilic attack of phosphorus at sulfur to give a thiophosphonium salt which undergoes ring closure to form a three-membered ring intermediate (eq 6), and direct formation of the three-membered ring intermediate through biphilic insertion of phosphorus (eq 3).[10] In separate studies Luckenbach, Szmant and Olah have shown that oxygen transfers from sulfoxides to phosphorus(III) require a Lewis acid and have proposed mechanisms with electrophilic or nucleophilic attack by phosphorus at oxygen (eq 5).[11−13] The geometrical dependence of oxygen transfer in these reactions has not been determined.

We have previously used the endocyclic restriction test to provide evidence that the transfer of oxygen from a hydroxylamine to the phosphorus(III) of an arylphosphine does not follow a classic S_N2 pathway at either oxygen or nitrogen (eqs 1 and 2) and is not a biphilic insertion (eq 3) nor a radical reaction (eq 4). We proposed that the mechanism involves oxygen addition to phosphorus via a pentavalent phosphorane (eq 5).[14]

We now report application of the endocyclic restriction test to formal transfers of oxygen from the nitrone, an acetylhydroxylamine, and sulfoxide groups to phosphorus(III). The geometrical dependence of the transfer is evaluated by the reaction shown in general form in eq 8. If direct transfer can



(8)

occur at an oblique phosphorus−oxygen−heteroatom angle, the reaction should be intramolecular when the tether is short and n is a small number. If a large phosphorus−oxygen−heteroatom angle is required for direct transfer, the reaction will be intermolecular for short tethers and intramolecular for long tethers.[2,15] The present work illustrates the information that can be gained for three different reactions in which $n = 1$.

Results and Discussion

Transfer of Oxygen from a Nitrone to Phosphorus(III). The substrates **1**, **5**, and **6** have been used to investigate the transfer of oxygen from a nitrone to phosphorus(III). The syntheses of **1**, **5**, and **6** were carried out by modification of the synthesis of 2-(diphenylphosphino)benzaldehyde reported by Rauchfuss.[16] Protection of 2-bromobenzaldehyde with ethylene glycol afforded the corresponding 2-bromodioxolane. Conversion to the Grignard reagent and treatment with the appropriate diarylphosphinous chloride gave the corresponding phosphine which was deprotected and condensed with *N-tert*-butylhydroxylamine to provide the nitrones **1, 5**, and **6**. An X-ray crystallographic structure of **1** established that the oxygen and the aryl ring bearing the triarylphosphine are syn disposed (Figure 1). Synthesis of doubly labeled **1**-^{13}C,^{18}O for the endocyclic restriction test (vide infra) was carried out by lithiation of (2-bromophenyl)diphenylphosphine with *t*-BuLi followed by reaction with methyl formate-^{13}C to give labeled aldehyde. Reaction of the aldehyde with *N-tert*-butylhydroxylamine-^{18}O afforded **1**-^{13}C,^{18}O.[17,18]

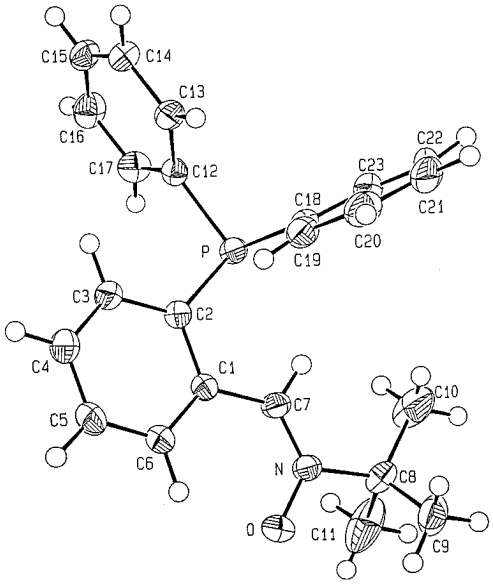
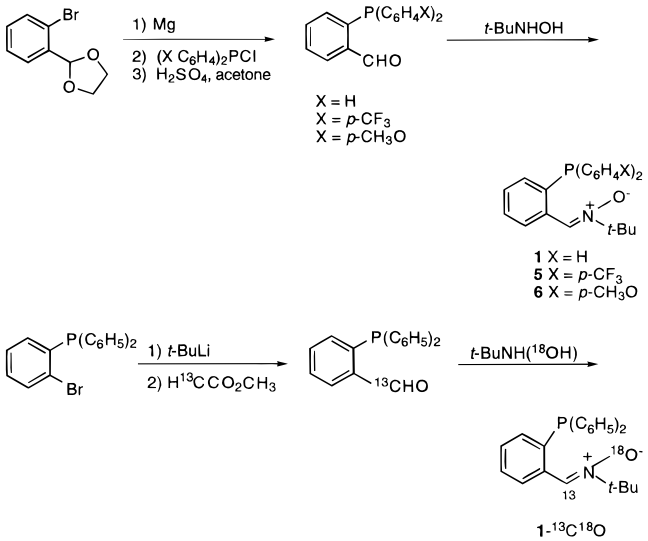


Figure 1. Crystallographic structure of **1**.



The transfer of oxygen from nitrogen to phosphorus(III) occurs on heating **1** at 110 °C for 57 h in toluene to give phosphine oxide **2**. This product was not isolable in pure form but was identified by its spectral properties. Crude **2** was converted by reduction to **3** and by hydrolysis on chromatography to **4**. An authentic sample of **3** was prepared by reaction of **4** with *tert*-butyl amine followed by reduction. On heating in toluene, compounds **5** and **6** were converted to the imine−phosphine oxides **7** and **8**, respectively, and these imines were hydrolyzed to the corresponding benzaldehydes **9** and **10**.

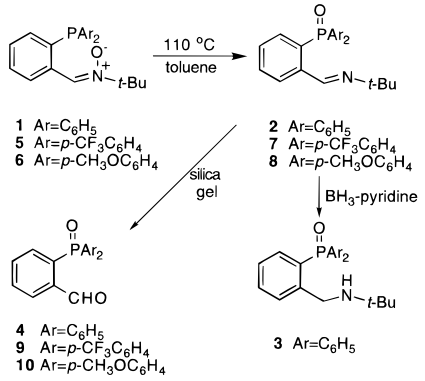
(14) Kurtzweil, M. L.; Loo, D.; Beak, P. *J. Am. Chem. Soc.* **1993**, *115*, 421.

(15) In addition to the seminal work of Eschenmoser and Hogg cited for the endocyclic restriction test, we want to include a number of other precedents which have been brought to our attention:[2] Cruickshank, P.; Fishman, M. *J. Org. Chem.* **1969**, *34*, 6061. Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349. Danishefsky, S.; Dynak, J.; Hatch, W. E.; Yamamoto, M. *J. Am. Chem. Soc.* **1974**, *96*, 1256. Lok, R.; Howard, J. K. *Bioorg. Chem.* **1976**, *5*, 169.

(16) Hoots, J. E.; Rauchfuss, T. B.; Wrobleski, D. A. *Inorg. Synth.* **1982**, *21*, 175.

(17) Woods, K. W.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 6281.

(18) There is 4% **1**-^{13}C,^{16}O in the doubly-labeled reactant.



The molecularity of the conversion of **1** to **2** was determined by double labeling experiments carried out with **1** and **1**-^{13}C,^{18}O as outlined in Scheme 1. If the reaction is intramolecular, the label integrity of the reactants will be preserved to give **2** and **2**-^{13}C,^{18}O in the same isomeric ratio as the reactants **1** and **1**-^{13}C,^{18}O, and provide **4** and **4**-^{13}C,^{18}O. If the reaction is intermolecular, then four products, **2**, **2**-^{13}C, **2**-^{18}O, and **2**-^{13}C,^{18}O, will be obtained with a statistical distribution of the isotopic labels, and lead to **4**, **4**-^{13}C,^{18}O, **4**-^{13}C, and **4**-^{18}O.

A 59:36 mixture of **1** and **1**-^{13}C,^{18}O in toluene at a combined concentration of 0.075 M was heated at 100 °C for 18 hours.[15] Purification of the product mixture by chromatography on silica gave **4** as the hydrolysis product of **2** along with unreacted **1**. Table 1 shows the results expected for intramolecular and intermolecular oxygen transfers and the experimental isotopic distributions for **4** as determined by FI/MS. A similar distribution was obtained in an additional double labeling experiment carried out for 20 h.

The results in Table 1 establish that oxygen transfer is an intramolecular reaction in the conversion of **1** to **2**. Therefore, the geometry of a classic S_N2 attack by phosphorus at oxygen (eq 1) does not have to be available for reaction because the constraints of the six-membered endocyclic ring would not allow a linear P−O−N geometry.[2,3] A classic S_N2 reaction at the nitrogen (eq 2) would require a front side displacement at an sp^2 atom which seems unlikely. The operations of a biphilic insertion or in-cage radical recombination (eqs 3 and 4) are not ruled out by the data but seem less likely than the alternatives (vide infra). This labeling result does rule out the possibility of an intermolecular oxygen transfer by a radical chain mechanism initiated by an adventitious radical source or by N−O bond cleavage.

Three mechanisms which are consistent with intramolecular transfer of oxygen in the conversion of **1** to **2** are shown in Scheme 2. In mechanism A, which is a specific case of eq 6, phosphorus attack at nitrogen to form intermediate **11** is followed by oxygen−phosphorus bond formation to give intermediate **12.** Cleavage of the P−N and N−O bond of **12** gives **2**. Mechanism B, which derives from eq 7, involves initial addition by phosphorus to the iminyl carbon, leading to **13**.[6] Subsequent addition of oxygen to phosphorus provides **14** which undergoes bond cleavage to **2**. In mechanism C, which is an example of eq 5, initial attack by oxygen at phosphorus gives **15**, which upon subsequent N−O bond cleavage provides **2**.[8]

If it is assumed that the first step of these mechanisms is rate determining, substituent effects may be used to distinguish between the possibilities.[19] In mechanisms A and B, there is

Scheme 1

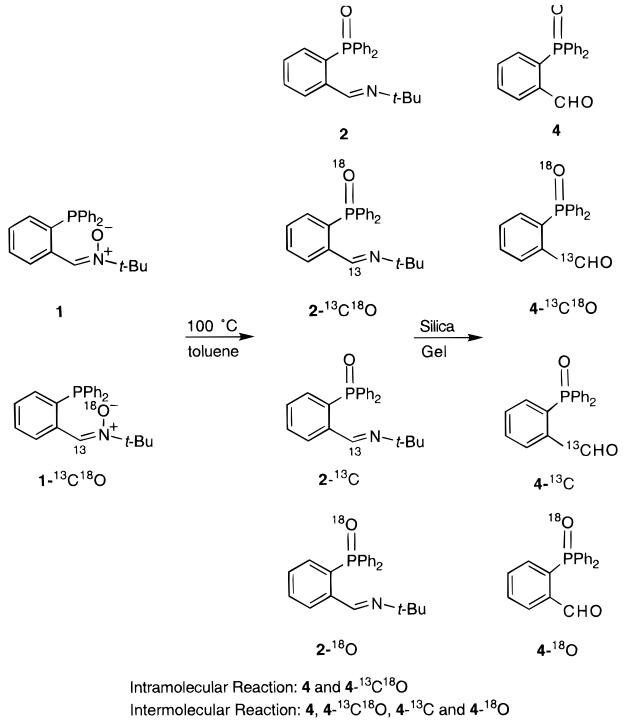
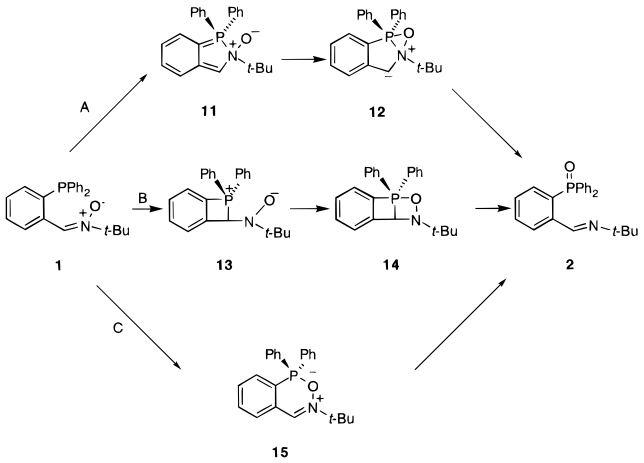


Table 1. Isotopic Distribution of **1** and **4** for the Double Labeling Experiment with **1** in Toluene at 100 °C[a]

label	reactant **1**	theoretical intramolecular	theoretical intermolecular	experiment **4**
$^{12}C^{16}O$	59	59	38	56
$^{13}C^{16}O$	4	4	25	7
$^{12}C^{18}O$	1	1	22	1
$^{13}C^{18}O$	36	36	15	36

[a] Error is estimated to be ±5% for the FIMS analysis.

Scheme 2



electron donation by phosphorus in the first step, whereas in mechanism C, phosphorus accepts electrons. Consequently, electron-donating groups on the aryl rings which are bonded only to phosphorus should accelerate oxygen transfer and electron-withdrawing groups should decelerate the transfer by mechanisms A and B. The opposite order of substituent effects would be expected for mechanism C.

We have carried out a limited substituent effect study with substrates **1**, **5**, and **6.** The CF_3 and CH_3O groups were chosen because they would be expected to have large effects on the relative rates of oxygen transfer. The conversions of **1** to **2** , **5** to **7**, and **6** to **8** were followed by NMR at 100 °C. First-order kinetics were observed for each reactant with values of k_{obs}

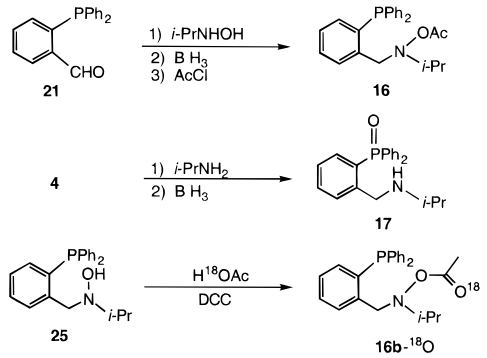
(19) Hammett studies have been used to distinguish between alternative mechanisms for reactions at phosphorus with absolute values of ρ as low as 0.35: (a) Sundberg, R. J.; Lang, C. *J. Org. Chem.* **1971**, *36*, 300. (b) Shulman, J. I. *J. Org. Chem.* **1977**, *42*, 3970. (c) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1984**, *49*, 793. (d) Lloyd, J. R.; Lowther, N.; Hall, C. D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 245. (e) Jarvis, B. B.; Marien, B. A. *J. Org. Chem.* **1976**, *41*, 2182.

($\times 10^{-2}$ h^{-1}) of 1.99 (±0.15), 7.2 (±1.3), and 1.59 (±0.07) for **1**, **5**, and **6**, respectively. The relative rate order of **5** > **1** > **6** is consistent with pathway C and inconsistent with pathways A and B.[20]

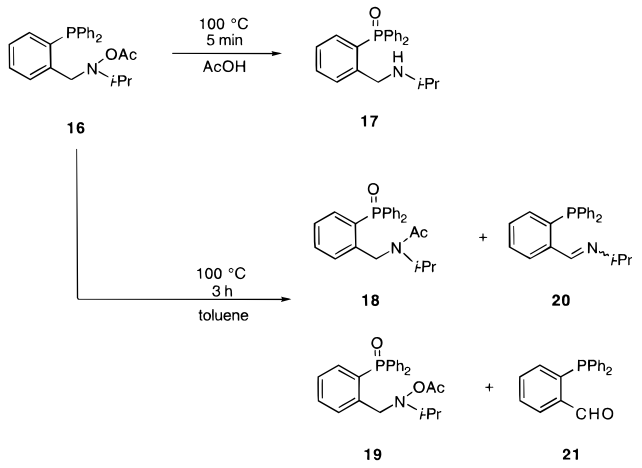
These results provide the first determination of the geometry of transfer of a formally negative oxygen to phosphorus. It should be noted that the endocyclic restriction test is permissive only; it establishes that the oxygen of a nitrone can be transferred to phosphorus at an oblique angle. Recent calculations which favor a large P−O−N bond angle for the transition state structure for this transfer suggest further studies to determine the preferred pathway are warranted.[21] It also is interesting to note that the X-ray structure of **1** (Figure 1) which has a close approach of the phosphorus to the nitrogen and a large separation of the phorphorus and oxygen might have been taken to predict reaction via **13**. In this case the structure−reaction correlation model would not have been useful.[22]

Transfer of Oxygen from an *O*-Acetylhydroxylamine to Phosphorus(III). The transfer of oxygen from an acetoxy group on nitrogen to phosphorus(III) has been investigated with **16**. The products obtained by heating **16** under different conditions are **17**−**21**.

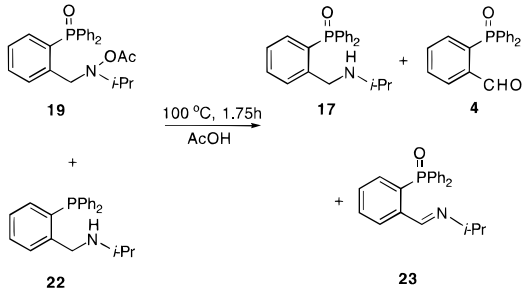
The *O*-acetylhydroxylamine **16** was synthesized from **21** by reaction with *N*-isopropylhydroxylamine, reduction, and acetylation. Independent syntheses of **17** and **18** were accomplished by treatment of **4** with *N*-isopropylamine followed by reduction to give **17** and by acetylation of **17** to give **18**. Compound **19** was synthesized by treatment of **4** with isopropylhydroxylamine followed by reduction and subsequent acetylation. The synthesis of **22** (vide infra) was accomplished by treatment of **21** with isopropylamine followed by reduction. Both **16a**-^{18}O and **16b**-^{18}O were prepared for labeling studies (vide infra). Treatment of **4** with *N*-isopropylhydroxylamine-^{18}O followed by reduction and acetylation gave **16a**-^{18}O with 74% enrichment. Labeled **16b**-^{18}O was prepared with 24% incorporation by treatment of **25** with acetic acid-^{18}O in the presence of DCC.



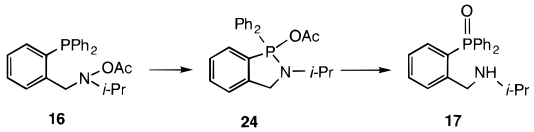
Oxygen transfer appears to occur in the conversion of **16** to **17**. When **16** is heated in acetic acid at 100 °C, **17** is produced. Heating **16** in toluene at 100 °C affords a more complex product mixture containing **18** (20%), **19** (20%), and **20** (45%) on the basis of NMR analysis. Another experiment in toluene from which the products were isolated gave **18**, **20**, and the hydrolysis product **21** in 9%, 32%, and 29% yields, respectively.[23]



The kinetics of the conversion of **16** to **17** were measured in deuterioacetic acid at 40 °C. The reaction is first-order with a rate constant of $(9.76 \pm 0.54) \times 10^{-2}$ min^{-1} ($r^2 = 0.992$). The potential intermediates for a bimolecular reaction of **16** with itself were tested for kinetic competence. When an acetic acid solution of **19** and **22**, 0.075 M in each, was heated at 100 °C for 1.75 h, only a minor amount of **17**, along with major amounts of **4**, **23**, and unreacted **22**, was detected by ^{1}H NMR. Thus, the kinetics, as well as the product profile on exposure of possible intermediates to the reaction conditions, rule out a classic bimolecular S_N2 reaction.[24] These results also rule out a radical chain reaction which would be greater than first order in **16** if initiated by **16**.



The reaction mechanism could involve **24** formed via a classic intramolecular S_N2 reaction by phosphorus at nitrogen followed by addition of acetate to phosphorus or by direct biphilic insertion.[19,25] The intermediate **24** could then lose an acetyl group and undergo ring opening to **17**. This possibility was investigated initially by ^{18}O-labeling experiments.



When **16a**-^{18}O was heated in acetic acid at 100 °C for 1.75 h, the product **17** obtained after aqueous workup was found by

(20) The possibility that the steps **11** to **12** to **2** or **13** to **14** to **2** are the rate-determining steps or that **12** and **14** are formed directly cannot be ruled out definitively. However, since those mechanisms are more complex and not required by the data, mechanism C is preferred.

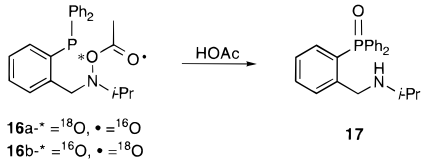
(21) Bachrach, S. M. *J. Org. Chem.* **1990**, *55*, 1016.

(22) Rosenfield, R. E., Jr.; Parhasarathy, R.; Dunitz, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 4860. Burgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153. Burgi, H. D.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. Cases have been discussed for which the X-ray structure does not indicate a probable reaction trajectory: Venvogoplan, P.; Venkatesan, K.; Klausen, J.; Novotny-Bregger, E.; Leuman, C.; Eschemoser, A.; Dunitz, J. D. *Helv. Chem. Acta* **1991**, *74*, 662.

(23) The isolation experiment was carried out by D. K. Loo: Loo, D. K. Ph.D. Thesis, University of Illinois at Champaign-Urbana, 1987 (available from Dissertation Abstracts, Ann Arbor, MI). The differences between the NMR and isolation experiments are attributed to hydrolysis during the latter and the possible presence of **22** in the former which was not detected due to overlapping signals.

(24) The S_N2 mechanism proposed for reaction of the O−O linkage in diacyl peroxides with phosphorus has been tested kinetically: Greenbaum, M. A.; Denney, D. B.; Hoffman, A. K. *J. Am. Chem. Soc.* **1956**, *78*, 2563. Horner, L.; Jurgeleit, W. *Liebigs Ann. Chem.* **1955**, *591*, 138.

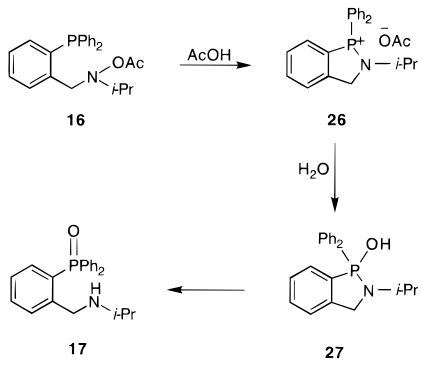
mass spectral analysis to have no excess ^{18}O over natural abundance. Reactions of **16a** and **16b** were carried out at 56 °C to allow for the recovery of reactant along with the formation of product. Both reactants were found to have full label integrity, and **17** from either labeled reactant **16a** or **16b** was found to contain no detectable level of ^{18}O isotopic enrichment. A control experiment showed that ^{18}O label was not lost from the product under the reaction or workup conditions. To test the possibility that the loss of label occurred in an intermediate, which exchanges its label with the acetic acid, a reaction was carried out in which **16** was heated in acetic acid-^{18}O containing 60% $^{16}O_2$, 34% $^{16}O^{18}O$, and 6% $^{18}O_2$ label at 100 °C for 5 min.[25] Analysis of the product after aqueous workup showed that there was no excess ^{18}O incorporation in the **17** produced from this reaction.



16a-* $=^{18}O$, • $=^{16}O$
16b-* $=^{16}O$, • $=^{18}O$ **17**

Since neither the acetyl group of **16** nor the acetic acid solvent provides the oxygen which appears in **17** from the conversion of **16** to **17** in acetic acid, other sources for the oxygen were investigated. Air oxidation, as well as more complicated possibilities involving dioxygen, is possible.[26] However, when **16** was heated in AcOH saturated with 97% $^{18}O_2$ under an $^{18}O_2$ atmosphere at 100 °C for 10 min, **17** was obtained with no ^{18}O enrichment.

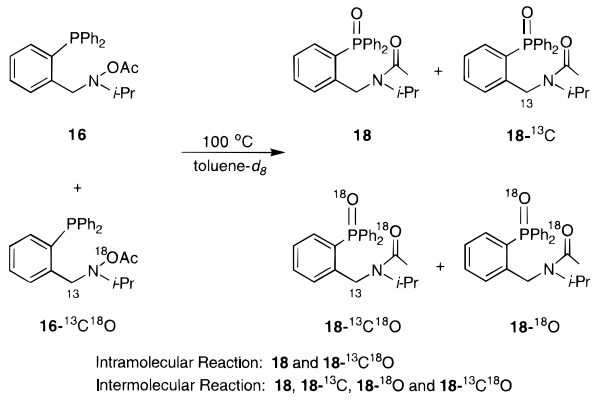
A mechanism consistent with the loss of label is displacement at nitrogen to give an intermediate, which is a stable species and does not react further in acetic acid. Thus, a displacement by phosphorus at the nitrogen of **16** could afford **26** as a stable species which subsequently reacts with water only on workup to give **27** that leads to **17**. Analogies for the stability of **26** may be found in the reaction of triphenylphosphine with an *O*-benzoylhydroxylamine to give a phosphorus−nitrogen ylide and in nucleophilic substitutions by triphenylphosphine and *O*-acyl-, *O*-phosphinyl-, or *O*-sulfonylhydroxylamines to give aminophosphonium salts.[7,27]



16 **26** **27** **17**

In order to test this mechanism, a reaction was carried out in which **16** was heated in AcOH at 100 °C for 5 min, followed by removal of the solvent. The residue was treated with an excess of $H_2{}^{18}O$ with 98% ^{18}O followed by $NaHCO_3$ to neutralize the residual AcOH. Mass spectral analysis showed the product from this sequence **17** to have 83% ^{18}O enrichment.[28]

Scheme 3



Direct evidence for **26** as a stable intermediate was obtained by ^{31}P NMR. When **16** is heated in acetic acid-d_4, a new ^{31}P NMR signal is observed at +50.7 ppm. The signal remains unchanged after 2 h at 100 °C. After several days at room temperature, a minor ^{31}P NMR signal which corresponds to that of **17** appears at +40.5 ppm. Thus, **26** is assigned to the ^{31}P NMR signal at 50.7 ppm. The salt **26** was isolated by removal of acetic acid in vacuo and shown to have ^{31}P chemical shifts of +50.2 ppm in methanol-*d* and +49.7 ppm in C_6D_6. This chemical shift assignment is consistent with the ^{31}P NMR chemical shift of +47.6 ppm ($CDCl_3$) for the isolable salt (dimethylamino)triphenylphosphonium chloride and also with assignments made by Evans and by Krannich for similar structures.[29−31]

The pathway for the conversion of **16** to **17** in toluene was also investigated. On heating **16** in toluene at 100 °C, the ^{31}P NMR of **16** at −15.1 ppm disappeared after 3 h. Signals for **20** appear at −12.1 ppm, along with four smaller signals in the region between +29 and +32 ppm which correspond to the phosphine oxides **18** and **19**, and an unidentified product. Two signals are attributed to **18** because of rotational isomerism about the imide bond. The ^{31}P NMR signal which is observed at +49.4 ppm is similar to the value of +49.7 in C_6D_6 for **26** (vide supra), and the same assignment is made. When toluene was added to **26**, prepared by removal of acetic acid (vide supra), and the reaction mixture heated at 100 °C for 3 h, **18** was obtained in 70% yield. Heating **16a**-^{18}O (74% ^{18}O) in toluene provided **18**-^{18}O with 71% ^{18}O enrichment. These results establish that **18** can be produced from **26** in toluene and that the oxygens on phosphorus and in the acetyl group come from the acetate.

When a mixture of doubly-labeled **16**-^{13}C,^{18}O and unlabeled **16** was heated in toluene, a statistical mixture of **18**, **18**-^{13}C, **18**-^{18}O, and **18**-^{13}C,^{18}O was obtained as shown in Scheme 3 and Table 2. The recovered reactant was found to have intact isotopic content, and a control study in acetic acid showed that the ^{18}O label was retained in the product (vide supra). These results can be taken to show label scrambling had not occurred

(25) Biphilic reactions have been proposed: Lloyd, J. R.; Lowther, N.; Hall, C. D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 245. Clennan, E. L.; Heah, P. C. *J. Org. Chem.* **1984**, *49*, 2284. Denney, D. B.; Denney, D. Z.; Hall, C. D.; Marsi, K. L. *J. Am. Chem. Soc.* **1972**, *94*, 245.

(26) Watts, G. B.; Ingold, K. V. *J. Am. Chem. Soc.* **1972**, *94*, 2528.

(27) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239. Harger, M. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3284. Krueger, J. H.; Sudbury, B. A.; Blanchet, P. F. *J. Am. Chem. Soc.* **1974**, *96*, 5733.

(28) Dilution of the ^{18}O label from 98% to 89% would be excepted for statistical redistribution of the ^{18}O into the $NaHCO_3$.

(29) Evans, S. A., Jr.; Pautard, A. M. *J. Org. Chem.* **1988**, *53*, 2300.

(30) Krannich, L. K.; Kajolia, R. K.; Watkins, C. L. *Org. Magn. Reson.* **1987**, *25*, 320.

(31) The possibility that **26** is in equilibrium with appreciable amounts of **24** is unlikely since phosphoranes containing a structure similar to **24** would be expected to have ^{31}P NMR chemical shifts from −10 to −70 ppm. For typical acyclic examples, see: Chang, L. L.; Denney, D. B.; Denney, D. Z.; Kazior, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 2293. For typical cyclic and spirobicyclic examples, see: Dennis, L. W.; Bartuska, V. J.; Maciel, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 230.

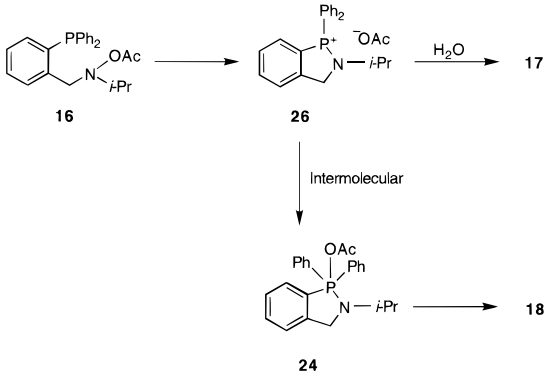
Table 2. Isotopic Distribution of **16** and **18** for the Double Labeling Experiment with **16** in Toluene at 100 °C

label	reactant **16**	theoretical intramolecular	theoretical intermolecular	experiment[a] **18**
$^{12}C^{16}O$	49	49	36	40
$^{13}C^{16}O$	17	17	29	29
$^{12}C^{18}O$	7	7	19	18
$^{13}C^{18}O$	28	28	15	12

[a] Error is estimated to be ±5% for the FIMS analysis.

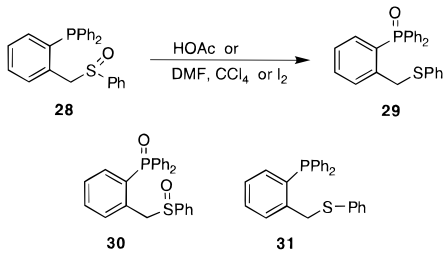
prior to or after oxygen transfer. The data in Table 2 show that the conversion of **16** to **18** in toluene involves intermolecular transfer of the oxygen from the acetoxy group to phosphorus.

Thus, the first step of the mechanisms for the conversion of **16** to **17** in acetic acid and to **18** in toluene is formation of the aminophosphonium salt **26**. In acetic acid, **26** provides **17** upon addition of water. In toluene, the phosphonium salt could add acetate to give **24**. Rearrangement of **24** with acyl transfer to nitrogen and ring opening could provide **18**. The question of whether the rearrangement of **24** to **18** is intramolecular or intermolecular is unresolved. In order for **24** to come directly from **16**, there would need to be a step which allows the observed isotopic scrambling. The product **19** is considered to be formed by oxidation by adventitious oxygen. The failure of **19** and **22** to provide products in toluene rules out these compounds as intermediates.[32]

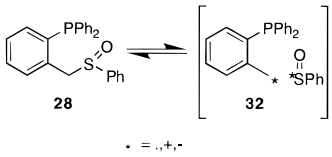


Transfer of Oxygen from a Sulfoxide to Phosphorus(III). The transfer of oxygen from sulfur to phosphorus(III) has been investigated for the conversion of **28** to **29** in acetic acid and in DMF, the latter with oxidative catalysis.[11−13,33] The synthesis of **28** was carried out by lithiation of diphenyl-*o*-tolylphosphine with *n*-BuLi/TMEDA followed by reaction with methyl benzenesulfinate. For **28**-^{13}C,^{18}O**,** diphenyl-*o*-tolylphosphine-^{13}C was synthesized from diphenyl(*o*-bromophenyl)phosphine by halogen−metal exchange with *n*-BuLi and reaction with $^{13}CH_3I$. The labeled compound was lithiated and allowed to react with methyl benzenesulfinate-^{18}O to provide **28**-^{13}C,^{18}O. The methyl benzenesulfinate-^{18}O was prepared from the sodium salt of benzenesulfinic acid by treatment with thionyl chloride, $H_2{}^{18}O$, and diazomethane sequentially. An authentic sample of **29** was prepared in two steps by lithiation of diphenyl-*o*-tolylphosphine with *n*-BuLi/TMEDA followed by addition of diphenyl disulfide to give **31**. Oxidation of **31** with 30% H_2O_2 led to **29**. The synthesis of enantiomerically enriched (*R*)-**28** (64% ee) (vide infra) was accomplished by reaction of lithiated diphenyl-*o*-tolylphosphine with enantiomerically enriched menthyl benzenesulfinate.[34,35]

When **28** is heated in acetic acid at 50 °C, **29** is produced in 85% yield. Although **28** is stable to heating in DMF at 80 °C for 4.5 h, when **28** is heated in DMF at 75 °C in the presence of 1 equiv of CCl_4 or I_2, **29** is produced along with a small amount of **30**. Oxidative promotion of this type of oxygen transfer reaction has been reported by Vedejs et al.[33]



Benzyl tolyl sulfoxide has been shown to undergo thermal racemization at sulfur at 135−155 °C by carbon−sulfur bond cleavage.[36] Although the reactions of **28** occur at 100 °C**,** a similar process with **28** would compromise any conclusion about transition structure geometry since the bond-breaking and bond-forming steps would be disassociated. The possibility of carbon−sulfur bond cleavage prior to oxygen transfer was addressed for **28** by exposure of enantioenriched **28** to the reaction conditions using Mislow's approach.[35] If the enantioenriched reactant is unchanged, then a mechanism involving carbon−sulfur bond cleavage and recombination prior to oxygen transfer is unlikely. If the reactant is racemized, then reversible formation of intermediate **32** is indicated.



Treatment of (*R*)-**28** (64% ee) in AcOH at 50 °C for 2 h and separately at 77 °C in DMF in the presence of CCl_4 for 2.3 h afforded 17% of unreacted **28** (66% ee) and 50% of unreacted (*R*)-**28** (70% ee), respectively. These results show that **28** is stable to racemization under the reaction conditions and the reversible formation of **32** can be discounted.

The conversion of **28** to **29** was found to follow first-order kinetics with a rate constant of $(9.10 \pm 0.54) \times 10^{-3}$ min^{-1} ($r^2 = 0.992$) for the reaction in deuterioacetic acid at 50 °C. This result rules out a classic S_N2 substitution at oxygen and a radical chain process.

In an attempted double-labeling experiment reaction of **28** and **28**-^{13}C,^{18}O in acetic acid, no ^{18}O label was observed in the product **29**.[37] To test for the possibility of a reaction intermediate which undergoes exchange under the reaction conditions, **28** was heated in acetic acid containing 60% $^{16}O_2$, 34% $^{16}O^{18}O$, and 6% $^{18}O_2$ label. The **29** isolated from this experiment had 20% ^{18}O incorporation as determined by FI/MS analysis. This

(32) The fact that the origin of the second oxygen in **19** is probably from adventitious oxygen dissolved in the solvent is supported by the reaction of **18a**-^{18}O with 78% ^{18}O to give **19**-^{18}O which has 79% ^{18}O. If both oxygens of **19** had come from the acetate, a detectable amount of **19**-$^{18}O_2$ would have been expected.

(33) Vedejs, E.; Mastalerz, H.; Meier, G. P.; Powell, D. W. *J. Org. Chem.* **1981**, *46*, 5253.

(34) Herbrandson, H. F.; Dickerson, R. T., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 4102.

(35) Pirkle, W. H.; Beare, S. D.; Muntz, R. L. *Tetrahedron Lett.* **1974**, 2295. Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1968**, *90*, 6250.

(36) Miller, E. G.; Rayner, D. R.; Thomas, H. T.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4861.

(37) A control experiment showed that labeled **29** was recovered with intact label after heating in acetic acid at 40 °C for 1.5 h. Reactant **28** recovered from the attempted double labeling experiment also appeared to show a retention of ^{18}O, suggesting exchange had not occurred prior to reaction. However, FAB/MS evaluation of the isotopic composition of **28** had errors due to some apparent exchange in the analysis which prevents an unambiguous conclusion.

Scheme 4

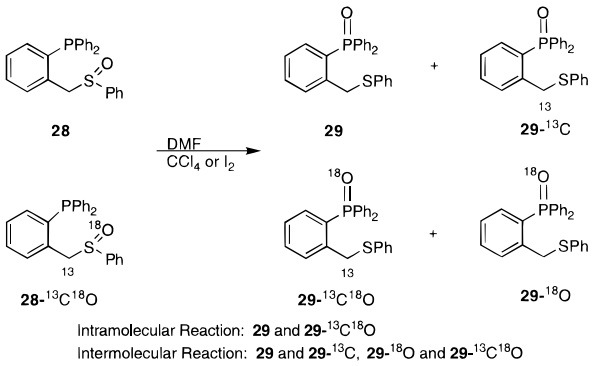
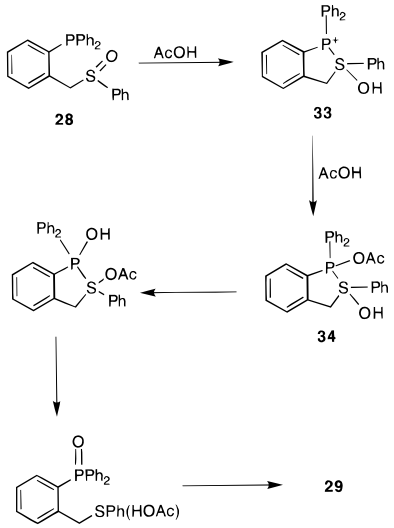


Table 3. Isotopic Distributions of **28** and **29** for the Double Labeling Experiments with **28** in DMF at 77 °C[a]

conditions	label	reactant **28**	theoretical[b] intramolecular	theoretical[b] intermolecular	experiment **29**
1 equiv of added CCl_4	$^{12}C^{16}O$	52	52	36	53
	$^{13}C^{16}O$	17	17	32	17
	$^{12}C^{18}O$	0	0	16	0
	$^{13}C^{18}O$	30	30	14	30
1 equiv of added I_2	$^{12}C^{16}O$	48	51	35	56
	$^{13}C^{16}O$	18	18	34	16
	$^{12}C^{18}O$	7	0	16	0
	$^{13}C^{18}O$	26	31	15	28

[a] Experimental error is estimated to be ±5% for isotopic distributions in **29** determined by FAB/MS. [b] For the I_2 case the theoretical intra- and intermolecular distributions were calculated on the basis of weighed amounts of unlabeled and doubly-labeled starting materials because FAB/MS of **28** did not give consistent results. The comparison of the columns for this reaction shows the deviation.

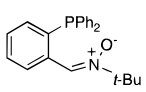
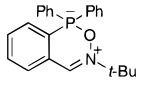
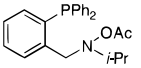
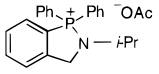
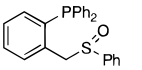
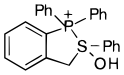
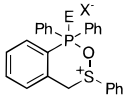
result is within experimental error of the 23% ^{18}O label expected on the basis of the statistical availability of ^{18}O label in the labeled acid. Analysis of recovered **28** showed no ^{18}O incorporation.[37] On the basis of these results, we suggest the formation of **33** which adds acetic acid to give **34** which leads to **29** by loss of acetic acid. This is consistent with the generalized case of eq 7.

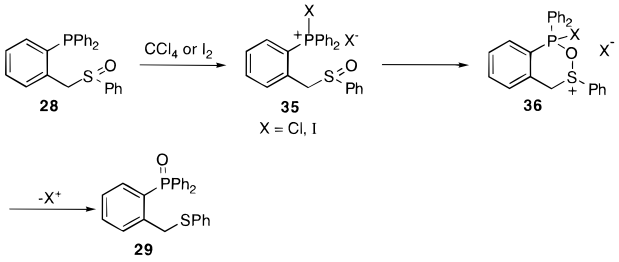


The conversion of **28** to **29** in DMF in the presence of CCl_4 or I_2 has been investigated by double-labeling experiments as shown in Scheme 4 and Table 3. The isotopic distribution in the products is the same as that in the reactants within experimental error, consistent with intramolecular oxygen transfer.

The conversion of **28** to **29** in DMF with CCl_4 or I_2 is consistent with initial halogenation at phosphorus to give **35** which undergoes ring closure to **36**. Loss of a positive halogen, perhaps to continue a chain, gives **29**. This mechanism is analogous to previous proposals for similar reactions such as generalized eq 5.[11,33,38]

Table 4. Reactants and Transition Structure For Oxygen Transfers to Phosphorus(III)

Reactant	Intermediate
	
1	15
	
16	26
	
28	33
	
	36



Summary. The mechanisms of oxygen transfer from a nitrone nitrogen, an *O*-acetylhydroxylamine nitrogen, and a sulfoxide sulfur to a phosphine phosphorus(III) have been investigated using the endocyclic restriction test, isotopic labeling, reaction kinetics, and NMR spectroscopy. The structures of the reactive intermediates which are consistent with the data are shown in Table 4. The transfer of oxygen from the nitrone to phosphorus involves valence expansion at phosphorus via intermediate **15**. This pathway is similar to oxygen transfer from the corresponding hydroxylamine and corresponds to eq 5.[2] A different pathway is followed for oxygen transfer from an *O*-acetylhydroxylamine, in which displacement at nitrogen occurs to give the intermediate **26** which is a precursor to **17** or **18** by reaction with water or acetate. The oxygen is indirectly transferred in these reactions. This pathway may result from the decreased ability of the oxygen of the acetate to bond to phosphorus and the increased leaving group ability of the acetate. This reaction is an example of eq 2. For the transfer of oxygen to phosphorus from sulfur, mechanisms involving phosphorus bonding to sulfur and oxygen through **33** and **36** are supported. These mechanisms represent the mechanisms of eqs 5 and 6. Clearly there is not a single general mechanism for transfer of oxygen from a heteroatom to phosphorus(III) and the pathways represented by eqs 1−7 provide a useful framework for understanding these reactions.

Experimental Section

General Methods. The ^{31}P NMR spectra were recorded on a GN-300NB spectrometer (121 MHz) in $CDCl_3$ using 85% H_3PO_4 as an external standard unless otherwise specified. Mass spectra were performed on Finnigan-MAT 311A and 731 or a Varian MAT CH-5 spectrometer with ionization energies of 10 or 70 eV by the University of Illinois Mass Spectrometry Laboratory. Data are reported in the

(38) Preux, M.; Lerous, Y.; Savignac, P. *Synthesis* **1974**, 506. Castrillon, J. P. A.; Szmant, H. H. *J. Org. Chem.* **1965**, *30*, 1338.

form *m/z* (area). Elemental analyses were performed by the University of Illinois Microanalytical Laboratory. Flash and medium-pressure (MP) liquid chromatographies were performed using Merck 50−200 mm and 32−63 mm silica gel, respectively. Preparative thin layer chromatography (Prep TLC) was performed on Kieselgel 60 F_{254} plates from Merck containing indicator with visualization by UV light. Analytical thin layer chromatography was performed on Merck silica plates with F-254 indicator. Visualization was accomplished by UV light or iodine. Analytical gas chromatography was performed on a HP 5790S or a HP 5890A chromatograph using a Hewlett-Packard fused silica capillary column cross-linked with 5% phenyl methyl silicone (column i.d. 0.20 mm; column length 25 m) equipped with a flame ionization detector. The injector temperature was 250 °C, and the detector temperature was 300 °C. When microanalysis data were not available, the purity of the title compound was judged to be >90% by ^{1}H NMR spectral determinations unless otherwise noted.

All solvents and reagents were obtained from commercial sources and used without further purification, except where noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone under an atmosphere of nitrogen. The ethyl acetate and hexane solvents used for MPLC and flash chromatography were distilled from bulk solvent over sodium carbonate and molecular sieves, respectively. Acetic acid was purified by treatment with acetic anhydride and distillation from CrO_3 as described by Perrin and Armarego[39] followed by distillation from Ph_3P under nitrogen. Dimethylformamide (DMF) was distilled from CaH under reduced pressure. ^{18}O-labeled water (10, 50, and 98+% ^{18}O) was purchased from Cambridge Isotope Labs or Isotec, Inc. Methyl formate-^{13}C (99% ^{13}C) was purchased from Isotec, Inc. Methyl-^{13}C iodide (99% ^{13}C) was purchased from Cambridge Isotope Labs. $^{18}O_2$ (98.9% ^{18}O) was purchased from Isotec.

All organometallic reagents used were obtained commercially and titrated according to the procedure of Tischler,[40] Shapiro,[41] or Suffert[42] prior to use. All reactions involving air- or water-sensitive reagents were carried out under nitrogen or argon in oven-dried or flame-dried glassware which was cooled under a nitrogen atmosphere.

Isotope ratios were detrermined either by FI/MS on a Finnigan MAT-731 instrument or by FAB/MS on a VG ZAB-SE instrument.[43]

α-*tert*-Butyl-2-(diphenylphosphino)benzenemethanimine *N*-Oxide (1). A mixture of 2-(diphenylphosphenyl)benzaldehyde (0.50 g, 1.7 mmol), *t*-BuNHOH−HCl (0.20 g, 1.6 mmol), and $CH_3CO_2^-Na^+$ (0.16 g, 2.0 mmol) in 83% EtOH−H_2O (30 mL) was stirred at room temperature for 24 h. The reaction was filtered to give 142 mg of recovered aldehyde as a yellow solid, mp 115.5−118.5 °C (lit.[17] mp 118−119 °C). The filtrate was diluted with CH_2Cl_2, and H_2O was added. The aqueous layer was back-extracted with CH_2Cl_2 (2×), and the combined organic layers were dried over Na_2SO_4. Concentration followed by chromatography (20% EtOAc−hexanes) gave 255 mg (44%) of **1** as a white solid after crystallization from 10% EtOAc−hexanes: mp 150.5-151.5 °C; ^{1}H NMR δ 9.25 (m, 1 H), 8.18 (d, J = 6.4 Hz, 1 H), 6.80−7.38 (m, 13 H), 1.36 (s, 9 H); ^{13}C NMR δ 128.19−137.33, 71.83, 28.44; ^{31}P NMR δ −10.3. Anal. Calcd for $C_{23}H_{24}NOP$: C, 76.43; H, 6.69; N, 3.88; P, 8.57. Found: C, 76.51; H, 6.80; N, 3.77; P, 8.43.

***N*-[2-(Diphenylphosphinyl)benzyl]-*N*-*tert*-butylamine (3).** A solution of **4** (151.4 mg, 0.49 mmol) and *t*-$BuNH_2$ (0.10 mL, 0.95 mmol) in EtOH (15 mL) was stirred at room temperature for 3 days. The reaction mixture was cooled to 0 °C, and BH_3−pyridine (0.25 mL, 2.5 mmol) was added via syringe. After warming slowly to room temperature over 20 h, 3 M HCl (20 mL) was added and stirring was continued overnight. The aqueous layer was extracted with CH_2Cl_2. The resulting organic layer was dried over Na_2SO_4 and concentrated to give a brown oil. The aqueous layer was treated with saturated Na_2CO_3 until basic and was then extracted with CH_2Cl_2 (3×). This organic layer was dried over Na_2SO_4 and concentrated to give a yellow tacky oil weighing 21 mg. ^{1}H NMR of this material gave a spectrum which was consistent with that of **3**. The product from the original organic layer was redissolved in CH_2Cl_2, washed with saturated $NaCO_3$, dried over Na_2SO_4, and concentrated to give a light brown oil weighing 196 mg which slowly began to crystallize. Preparative TLC (10% MeOH−EtOAc) of the combined organic fractions gave 78 mg (44%) of **3** as a light brown oil which eventually solidified. Trituration (EtOAc−hexanes) gave a fine solid from which the supernatant was removed. Concentration and trituration (10% EtOAc/hexanes) gave **3** as a waxy, light yellow solid: mp 86−90 °C; ^{1}H NMR δ 6.98−7.71 (m, 14 H), 3.81 (s, 3 H), 2.10 (br s, 1 H), 1.02 (s, 9 H); ^{13}C NMR δ 126.15−133.50, 45.58 (d, J = 3.7 Hz); ^{31}P NMR δ 32.8. Anal. Calcd for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.86; P, 8.52. Found: C, 76.35; H, 7.42; N, 3.49; P, 8.18.

α-*tert*-Butyl-2-[bis(4-trifluorophenyl)phosphino]benzenemethanimine N-Oxide (5). A mixture of the benzaldehyde (251 mg, 0.59 mmol), *t*-BuNHOH−HCl (81.7 mg, 0.65 mmol), and $CH_3CO_2^-Na^+-3H_2O$ (97 mg, 0.71 mmol) in 15 mL of 5:1 EtOH−H_2O was stirred at ambient temperature for 10 h. An additional 81 mg of the hydroxylamine was added along with 96 mg of $CH_3CO_2^-Na^+$. After 11.5 h the reaction was diluted with CH_2Cl_2 and washed with 10% NH_4Cl (50 mL) followed by H_2O (1×). The organic layer was dried over Na_2SO_4 and concentrated to give a yellow semisolid. Chromatography (20% EtOAc−hexanes) gave 98.3 mg of recovered aldehyde and 108.5 mg (37%) of **5** as an off-white solid: mp 152−154 °C; ^{1}H NMR δ 9.23 (m, 1 H), 8.24 (d, J = 6.4 Hz, 1 H), 7.26−7.65 (m, 10 H), 6.86 (m, 1 H), 1.40 (s, 9 H); ^{13}C NMR δ 121.16−140.10, 71.8, 28.1; ^{31}P NMR δ −12.1. Anal. Calcd for $C_{25}H_{22}F_6NOP$: C, 60.36; H, 4.46; N, 2.82; P, 6.23. Found: C, 60.45; H, 4.45; N, 2.66; P, 6.30.

α-*tert*-Butyl-2-[bis(4-methoxyphenyl)phosphino]benzenemethanimine *N*-Oxide (6). To a solution of the benzaldehyde (102 mg, 0.29 mmol) in 5:1 EtOH−H_2O (6 mL) was added $CH_3CO_2^-Na^+-3H_2O$ (60.5 mg, 0.44 mmol) followed by *t*-BuNHOH−HCl (48.0 mg, 0.38 mmol). After stirring at room temperature (RT) for 17 h, a light yellow precipitate had formed. The reaction mixture was filtered to give 49 mg (40%) of **6** as a light yellow solid, mp 162.5−163.5 °C. The filtrate was concentrated, redissolved in Et_2O, and dried over Na_2SO_4. Chromatography (30% EtOAc−hexanes) gave an additional 25 mg (60%) of **6** as an off-white solid: mp 158−160 °C; ^{1}H NMR δ 9.23 (m, 1 H), 8.24 (d, J = 6.4 Hz, 1 H), 6.87−7.45 (m, 11 H), 3.80 (s, 6 H), 1.38 (s, 9 H); ^{13}C NMR δ 160.5, 128.40−135.8, 114.4, 55.2, 28.0; ^{31}P NMR δ −13.9. Anal. Calcd for $C_{23}H_{28}NO_3P$: C, 71.24; H, 6.70; N, 3.32; P, 7.35. Found: C, 71.05; H, 6.70; N, 3.21; P, 7.31.

***N*-[2-(Diphenylphosphinyl)benzyl]-*N*-isopropylamine (17)** was prepared as previously described.[14] A solution of 0.35 g (1.0 mol) of *N*-[2-(diphenylphosphino)benzyl]-*N*-isopropylhydroxylamine in 10 mL of toluene was heated at reflux for 1 h under a nitrogen atmosphere. The solution was cooled to ambient temperature and evaporated in vacuo to provide a yellow oil which was purified on the Chromatotron with 5% methanol in ethyl acetate as an eluent to give 0.32 g (90%) of **17** as a pale yellow solid: mp 93−95 °C; ^{1}H NMR δ 6.8−7.8 (m, 14 H), 4.8 (br s, 1 H), 3.85 (s, 2 H), 2.62 (hept, 1 H, J = 6.3 Hz), 0.9 (d, 6 H), J = 6.3 Hz); ^{13}C NMR δ 145.6 (d, J_{PC} = 8.2 Hz), 133.9, 133.5, 133.3, 132.3, 132.2, 132.1, 131.9, 131.8, 131.7, 131.5, 130.0, 128.6, 128.5, 128.4, 126.3, 126.1, 50.1 (d, J_{PC} = 5.3 Hz), 48.0, 22.6. Anal. Calcd for $H_{22}H_{24}PNO$: C, 75.62; H, 6.92; N, 4.01; P, 8.87. Found: C, 75.28; H, 7.09; N, 3.92; P, 8.70.

A solution of **4** (0.75 g, 2.45 mmol) in EtOH (25 mL) containing isopropylamine (1.0 mL, 11.7 mmol) was stirred for 36 h at room temperature. The reaction was cooled with an ice bath, and BH_3−pyridine (1.7 mL, 16.8 mmol) was added under a nitrogen atmosphere. After 1 h the cooling bath was removed, and stirring was continued at ambient temperature for another 20 h. The mixture was cooled to 0 °C, 10% hydrochloric acid was added dropwise until hydrogen evolution ceased, and stirring was continued at ambient temperature overnight. The mixture was basified with Na_2CO_3 to pH ≈ 12 and extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried over anhydrous Na_2CO_3. Concentration of the organic layer in vacuo gave an orange oil, which was purified by column chromatography (50% EtOAc−hexanes followed by 10% MeOH−EtOAc) to give a light yellow solid. Recrystallization from EtOAc−hexanes gave 394 mg of **17** as an off-white solid, mp 95−98 °C. A second crop gave an

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additional 91.0 mg of **17**. The ^{31}P NMR ($CDCl_3$) δ 32.3, ^{1}H, NMR, and ^{13}C NMR correspond to those above.

***N*-[2-(Diphenylphosphino)benzyl]-*N*-isopropyl-*O*-acetylhydroxylamine (16).** To a solution of **25** (100 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) containing pyridine (0.04 mL, 4.94 mmol) and a catalytic amount of DMAP (<10 mg) was added acetyl chloride (30.5 mL, 4.29 mmol). After stirring for 20 min at room temperature, the reaction was treated with 10% NH_4Cl (5 mL). The aqueous layer was extracted once more with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and conentrated to give 116 mg of a light yellow oil. Flash chromatography (CH_2Cl_2) gave 94 mg (84%) of **16** as a light yellow oil which slowly crystallized on standing in the freezer: mp 50.5−52.5 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.83−7.75 (m, 14 H), 4.24 (d, J = 2.5 Hz, 2 H), 3.17 (m, J = 6.3 Hz, 1 H), 1.76 (s, 3 H), 1.08 (d, J = 6.3 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 127.2−141.4, 57.3, 56.6 (d, J_{PC} = 25.3 Hz), 19.7, 18.5; ^{31}P NMR ($CDCl_3$) δ −15.3. Anal. Calcd for $C_{24}H_{26}NO_2P$: C, 73.64; H, 6.70; N, 3.58; P, 7.91. Found: C, 73.77; H, 6.76; N, 3.51; P, 7.83.

To a solution of **25** (250 mg, 0.72 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added AcOH (0.12 mL, 2.10 mmol) followed by DCC (440 mg, 2.10 mmol). After 0.5 h the cooling bath was removed, and stirring was continued for 0.5 h at RT. The reaction was then treated with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. Concentration followed by chromatography (90% CH_2Cl_2−hexanes) gave 229 mg (81%) of **16** as a light yellow oil which was identical by ^{1}H NMR with **16** prepared by other routes.

Conversion of 16 to 17. A solution of **16** (22.3 mg, 0.057 mmol) in AcOH (0.76 mL) was heated at 100 °C for 1.75 h. The solvent was removed in vacuo, and the product was dissolved in CH_2Cl_2. The organic layer was washed with 10% $NaHCO_3$ and dried over Na_2SO_4. Evaporation of solvent gave 14 mg (70%) of an oil which slowly crystallized. The ^{1}H NMR spectrum of the product was identical to that of an authentic sample of **17**.

***N*-[2-(Diphenylphosphinyl)benzyl]-*N*-isopropylacetamide (18).** To a solution of **17** (0.100 g, 0.29 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added AcOH (49 mL, 0.78 mmol) followed by DCC (0.18 g, 0.87 mmol). After 0.5 h the cooling bath was removed, and the reaction was stirred for 4 h and allowed to stand for 20 h. Removal of solvent in vacuo gave a white foam which after column chromatography (EtOAc followed by 10% MeOH−EtOAc) gave 72.0 mg (64%) of **18** as a colorless tacky oil which eventually crystallized; mp 136.5−140.5 °C. Recrystallization from EtOAc−hexanes gave a white solid: mp 135.5−137.5 °C; ^{1}H NMR ($CDCl_3$, 200 MHz, observed as an approximate 2:1 ratio of rotational isomers) δ 7.00−7.77 (m, 14 H), 4.80 (s, 0.66 H), 4.78 (m, 0.66 H), 4.69 (s, 1.33 H), 4.10 (m, 0.33 H), 2.22 (s, 1 H), 1.81 (s, 2 H), 1.05 (d, J = 6.6 Hz, 2 H), 0.80 (d, J = 6.6 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 143.7, 126.2−133.6, 49.9, 49.5, 44.8−45.4, 19.5−22.3; ^{31}P NMR ($CDCl_3$, 121 MHz, observed as a pair of singlets in an approximate 1:2 ratio) δ 32.26, 32.97; HRES/MS for $C_{24}H_{26}NO_2P$, m/z calcd 391.1701, found 391.1702. Anal. Calcd for $C_{24}H_{26}NO_2P$: C, 73.64; H, 6.70; N, 3.58. Found: C, 73.12; H, 6.66; N, 3.56.

2-(Diphenylphosphino)benzyl Phenyl Sulfoxide (28). To a solution of *n*-BuLi in hexanes (2.4 mL, 5.4 mmol) and TMEDA (0.82 mL, 5.4 mmol) in hexanes (10 mL) was added a solution of (2-methylphenyl)diphenylphosphine (1.0 g, 3.62 mmol) dissolved in hexanes (10 mL). After stirring for 1 h at ambient temperature, the orange heterogeneous mixture was cooled to −78 °C and a solution of methyl benzenesulfinate (1.15 g, 7.4 mmol) in Et_2O (5 mL) was added. The reaction was stirred for 15 min, and then the cooling bath was replaced with a 0 °C bath and allowed to warm slowly to ambient temperature over 10.5 h before H_2O and Et_2O were added. The resulting aqueous layer was back-extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$. Concentration in vacuo gave 2.0 g of a peach-colored oil which was redissolved in Et_2O and dry loaded into silica gel. Elution with a gradient of hexanes, 20% EtOAc−hexanes and 50% EtOAc−hexanes, gave a partially purified product. Additional purification of the Chromatotron (31% EtOAc−hexanes) gave 0.577 g (31%) of **28** as a colorless tacky oil which eventually solidified. Recrystallization from EtOAc−hexanes gave an analytical sample: mp 114−116 °C; ^{1}H NMR ($CDCl_3$) δ 6.98−7.67 (m, 19 H), 4.48 (dd, J = 13.0 Hz, 1.6, 1 H), 4.27 (d, J = 13.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 124.2−143.7, 63.3 (d, J = 21.1 Hz); ^{31}P ($CDCl_3$) δ −15.9; FI/MS m/z 310 (M^+). Anal. Calcd for $C_{25}H_{21}OPS$: C, 74.98; H, 5.29; P, 7.73; S, 8.01. Found: C, 74.83; H, 5.35; P, 7.64; S, 7.92.

2-(Diphenylphosphinyl)benzyl Phenyl Sulfide (29). To a mixture of **31** (151.2 mg, 0.29 mmol) in MeOH (25 mL) at 0 °C was added 30% H_2O_2 (31 mL, 0.35 mmol). After 0.5 h the cooling bath was removed, and a solution of the reaction was attained within 0.5 h at room temperature. Column chromatography (30% EtOAc−hexanes) gave 128 mg (82%) of **29** as a colorless oil. Trituration in hexanes gave a white solid, mp 108−111 °C. The ^{1}H NMR spectrum was identical with that of a sample obtained by oxygen transfer from **28**. An analytical sample of **29** was prepared by recrystallization from EtOAc−hexanes to give a white solid: mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 7.10−7.72 (m, 19 H), 4.58 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 125.79−142.47, 36.49 (d, J_{PC} = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ 32.6. Anal. Calcd for $C_{25}H_{21}OPS$: C, 74.98; H, 5.29; P, 7.73; S, 8.01. Found: C, 75.01; H, 5.30; P, 7.65; S, 7.94.

Conversion of 28 to 29 Using AcOH. A solution of **28** (28 mg, 0.07 mmol) in AcOH (0.70 mL) was heated in an NMR tube at 31 °C for 13 h. The reaction was diluted with CH_2Cl_2, and the acid was neutralized with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated to give 24 mg (85%) of **29** as an oil which was identical to an authentic sample as judged by ^{1}H NMR.

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Supporting Information Available: Text describing the syntheses of **21**, (*R*)-**28**, and labeled compounds and control experiments and tables listing crystallographic data, bond lengths and angles, positional and thermal parameters, and kinetic data (49 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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