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The Invention of Radical Reactions. Part 39. The Reaction of White Phosphorus with Carbon-Centered Radicals. An Improved Procedure for the Synthesis of Phosphonic Acids and Further Mechanistic Insights.[1]

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In memory of Professor Wang Yu, the great master of Chinese Organic Chemistry.

Abstract: White phosphorus in tetrahydrofuran under argon reacts in a long radical chain reaction with carbon radicals derived from Barton PTOC esters. The reaction is initiated by traces of oxygen and strongly inhibited by TEMPO. From the duration of the induction period the chain length can be measured as approximately one million. Each P_4 molecule can add up to two carbon radicals. Oxidation of the adducts provides a convenient synthesis of phosphonic acids in high yield. With H_2O_2 at 0°C oxidation to the appropriate phosphinic acids is fast. For sensitive natural products the further transformation to phosphonic acids is best carried out at room temperature with an excess of SO_2. In this way even linoleic acid can be converted to the corresponding phosphonic acid in good yield without any attack on the skipped diene unit. TEMPO is also remarkable for its stabilization of white phosphorus in solution when exposed to oxygen. Likewise an ordinary phosphine, like tributyl phosphine, is also stabilized by small amounts of TEMPO.

We recently communicated[2] that elemental white phosphorus (P_4) was a surprisingly inefficient reductant. However, it readily trapped carbon-centered radicals generated from carboxylic acids via photolysis of the corresponding Barton PTOC esters **2** in a CH_2Cl_2 / CS_2 binary mixture. Oxidation of the products of this reaction with aqueous hydrogen peroxide afforded phosphonic acids **3** in yields ranging from 71 to 86% (**Scheme 1**). The importance of such a simple procedure for the introduction of a phosphonic acid moiety is significant since many such derivatives have important biological activity.[3] Of mechanistic interest was the determination of a quantum yield of about 600 for the photolytic reaction.

Herein we report that modification of our initial experimental procedure provides a more efficient and higher yielding synthesis of phosphonic acids **3** from Barton PTOC esters **2**. Furthermore, these changes

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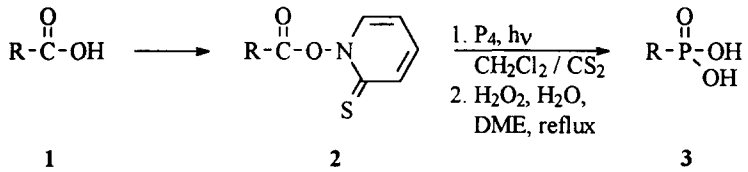
provide greater insight into the intermediates involved and allow a clearer mechanistic picture to be proposed. This methodology is also applicable to the introduction of the phosphonic acid moiety into sensitive natural products.



1 2 3

Scheme 1

RESULTS AND DISCUSSION

Mechanistic Studies

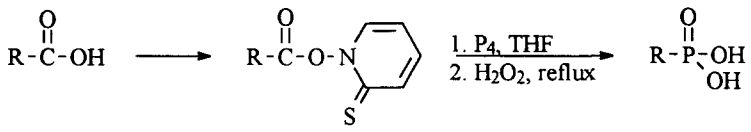
The original experiments[2] were carried out by photolysis of the Barton ester until all had been consumed. Since the usual rearrangement product, where R would be attached to the 2-thiopyridyl residue[4], could not be detected, the radical should have reacted quantitatively with the white phosphorus. However, the yields as determined by phosphorus NMR were not as elevated as expected. A thorough investigation of the reaction sequence revealed that the use of CS_2 was causing the reduced yields. We decided to replace the CH_2Cl_2 / CS_2 binary mixture with THF and to our surprise as soon as the Barton ester was added to the P_4 solution carbon dioxide was evolved, accompanied by a color change. Furthermore, the reaction was found to be complete in less than one minute even in complete darkness. Clearly, the reaction with THF as the solvent was being initiated by an unknown radical initiator while that which we reported previously in the CH_2Cl_2 / CS_2 binary mixture was being inhibited since irradiation was necessary for the reaction to take place.[2] Subsequent experiments revealed that CS_2 was behaving as an inhibitor by yielding minor amounts of termination products and lowering the chain length, which nevertheless remained impressive.

With this phenomenon highlighted we felt it beneficial to repeat a number of the reactions we reported previously[2] using THF as the solvent (**Table 1**). Evolution of CO_2 was spontaneous upon addition of each individual Barton ester to the solution of P_4 in THF. The reactions were complete within a few minutes and the isolated yields, after oxidation with aqueous H_2O_2, of the phosphonic acids were consistently higher than those found previously. The phosphonic acid of 4,4-dimethylpentanoic acid **3d** was also prepared in excellent yield (**Table 1**, Entry 4). Additionally, ^{31}P-NMR analysis showed that all the reactions were yielding the phosphonic acids quantitatively, a result consistent with the fact that no RS-2-Py was produced. Furthermore, whereas two equivalents of P_4 were previously necessary to ensure complete capture of the alkyl radicals, one equivalent was found to be sufficient under the new improved conditions.

Table 1. Comparison of Improved Procedure to Previous Method of Phosphonic Acid Synthesis.

Entry	Starting Material	Product (% yield)[a]	m.p. °C (lit.)	^{31}P-NMR[b] (solvent)
1	2a	3a (91) [74]	133-134 (137-138)[5]	31 (acetone)
2	2b	3b (90) [73]	165-167 (167-168)[6]	30 (DMSO)
3	2c	3c (96) [86]	297-300 (308-310)[7]	31 (DMSO)
4	2d	3d (80)	190-195	31 (DMSO)

[a] ( ) isolated yields relative to Barton PTOC esters **2**, [ ] previously reported yields.[2] [b] ^{31}P-NMR chemical shifts (ppm) referenced to external 85% H_3PO_4.



1 **2** **3**

a R = $PhCH_2CH_2$ **c** R = 1-adamantyl
b = cyclohexyl **d** = $(CH_3)_3CCH_2CH_2$

All the reactions performed in **Table 1** did not require initiation by irradiation nor were the yields affected by executing the reactions in the dark. In order to verify that some initiator was indeed starting the radical chain we studied the effect of TEMPO (2,2,6,6-TetraMethylPiperidyl-*N*-Oxyl) on the reaction. As summarized in **Table 2**, TEMPO had a dramatic effect in inhibiting the reaction and verified that radicals were indeed involved. The quenching of aliquots taken from the reaction mixture at specific time intervals with *n*-butylamine proved to be a convenient reagent for monitoring these reactions since it rapidly reacts with the Barton esters affording the corresponding stable amides, thus stopping the reaction. Analysis by thin layer chromatography (TLC) of the quenched aliquots proved to be a suitable method for estimating the end of the induction period. Noticeable changes in the TLC pattern, such as the formation of new spots, represented the end of the induction period, *i.e.* all of the TEMPO had been consumed. Without added TEMPO the reaction was complete within one minute at ambient temperature (**Table 2**, Entry 1). The addition of 0.00025 equivalents of TEMPO (**Table 2**, Entry 2) inhibited the reaction for about 270 minutes while 0.001 slowed the reaction even more dramatically (approximately 15 hours).

Performing the same reactions in the presence of air greatly reduced the inhibition period (**Table 2**, Entry 3) revealing that these reactions were actually initiated by the reaction of dioxygen with P_4. Performing the

entire reaction sequence in air simply led to a reduced yield of the desired phosphonic acid and the formation of significant quantities of phosphoric acid. Thus while trace amounts of dioxygen are essential to initiate the radical chain reaction, significant quantities of dioxygen are detrimental. Using the inhibition time and the amount of TEMPO employed the length of the radical chain was estimated[8] to be approximately 1,000,000. These findings are consistent with those found by Walling and co-workers[9] during the preparation of phosphonic acid derivatives from phosphorus, dioxygen, and olefins. Although their reactions were complex and low yielding, experimental results suggested that the mechanism involved attack of a radical containing the partial structure (P-O•) upon the olefin.

Table 2. The effect of TEMPO on the reaction between **2a** and P_4 in THF.

Entry	TEMPO (equivalents)	Inhibition Time (min.)
1	0	< 1 (reaction length)
2	0.00025 (argon)	270
3	0.001 (air)	5

Mechanistically, it is conceivable that more than one alkyl radical (R•) may add to each P_4 molecule. To answer this question , the amount of Barton ester **2a** was varied (0-2.5 equivalents) while keeping the quantity of P_4 constant (1 equivalent). Analysis of each reaction by ^{31}P-NMR yielded the results displayed in **Figure 1** and suggests that the addition of the second alkyl radical to the P_4 subunit must be extremely facile as substantial amounts of P_4 remained after cessation of the reaction. For example , the reaction of one equivalent of P_4 with one equivalent of Barton ester **2a** resulted in complete consumption of the Barton ester (verified by TLC and by the addition of *n*-butylamine), however, 0.35 equivalents of P_4 remained. Furthermore, two equivalents of Barton ester **2a** nearly consumes all of the P_4 (1 equivalent) with only trace amounts of rearranged product ($PhCH_2CH_2S$-2-Py) being detected.

Oxidation of the products remaining after all of the Barton ester was consumed resulted in near quantitative phosphonic acid formation by ^{31}P-NMR for those reactions having a Barton ester to P_4 ratio ≤ 1. Additionally, as the Barton ester to P_4 ratio approached 2 small amounts of dialkylphosphonic acid as well as rearrangement product could be detected. However, not more than 20% dialkylphosphonic acid could be formed when greater than 2 equivalents (6-8 equivalents) of Barton ester were employed.

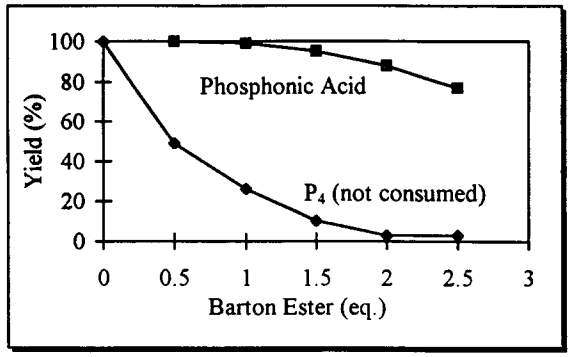
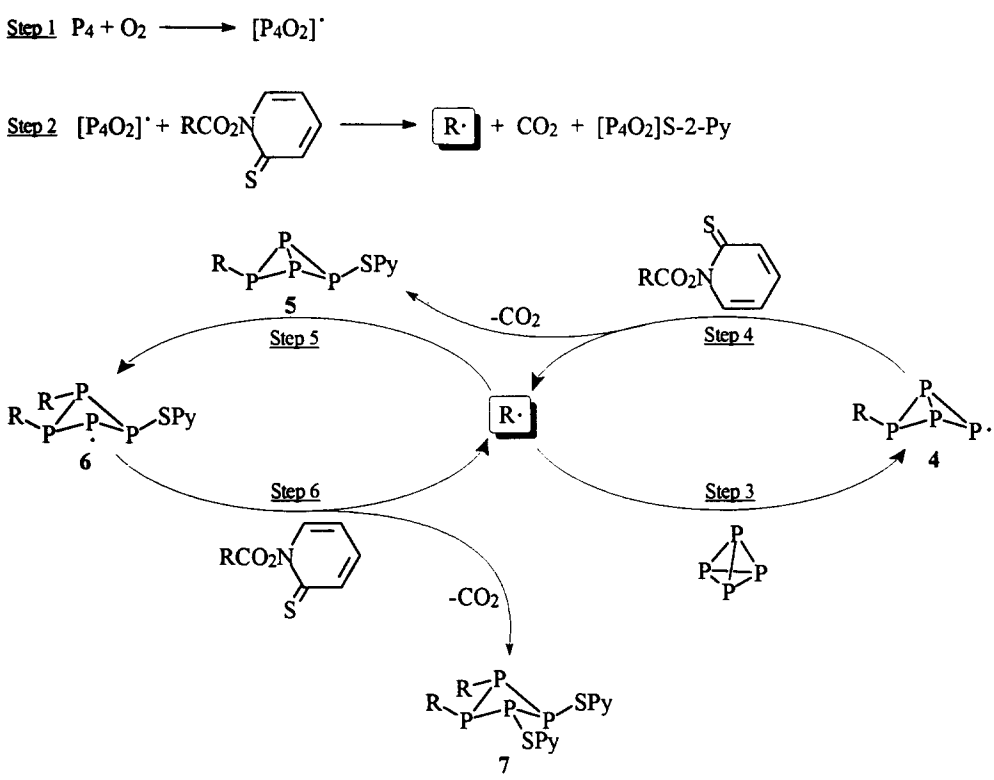


Figure 1. The reaction of P_4 (1 equiv.) with varying amounts of Barton ester **2a**



Scheme 2

The experimental information collated above allows a clearer mechanistic picture to be presented (**Scheme 2**) for the addition of carbon radicals to P_4. Although initiation normally results from irradiation of the Barton ester affording an alkyl radical (R•), carbon dioxide, and the thiopyridyl radical, initiation here results

from the reaction of dioxygen with P_4 (**Scheme 2**, step 1). The resulting radicals (exact structure unknown, but may contain the P-O• partial structure) react with Barton ester **2** and begin chain propagation as outlined in step 2 of **Scheme 2**. The resulting alkyl radicals (R•) are rapidly trapped by P_4 affording intermediate **4** which further propagates the chain by reacting with Barton ester **2** (**Scheme 2**, Steps 3 and 4) to give derivative **5**. As discussed above (**Figure 1**), the alkyl radicals react very fast with intermediate **5** affording **6** and finally the cyclotetraphosphine **7** as substantial amounts of P_4 remain after all the Barton ester **2** has been consumed (**Scheme 2**, Steps 5 and 6).

Modification of natural products

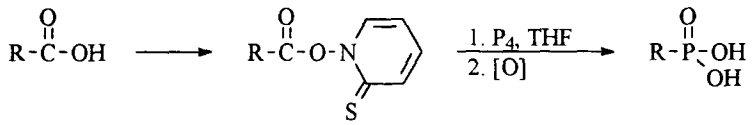
To further probe the scope of this procedure the phosphonic acid moiety was incorporated into several natural compounds with replacement of the appropriate carboxyl. At this point the procedure involved a rather harsh oxidation step (refluxing H_2O_2) that needed to be modified in order for the procedure to be compatible with unsaturated substrates. After an extensive search, we came upon an article[10] that described the oxidation of phosphines with sulfur dioxide (SO_2). As an added bonus SO_2 is a gas at room temperature and any excess can easily be removed thus facilitating purification of the product. Initial experiments showed great success as products were oxidized fully to the phosphonic acid while sensitive functional groups such as double bonds were not adversely affected. However, the work-up and isolation were unpleasant and messy because a polymeric substance of unknown composition was formed during the oxidation. This problem was not encountered when H_2O_2 was used as the oxidant, therefore we believed we could have the best of both worlds, a mild oxidation without a difficult work-up, if both oxidants were used consecutively. H_2O_2 will easily oxidize the intermediates at low temperatures (0°C) to the phosphinic acids. Refluxing is necessary for the H_2O_2 oxidation because the oxidation of the intermediate phosphinic acid to the phosphonic acid is rather difficult. SO_2 will easily oxidize the phosphinic acids to the phosphonic acids at low temperatures (room temperature). Thus making the oxidation a two-step process, H_2O_2 at 0°C then SO_2 at room temperature, should provide a mild and clean method of oxidation, and this was indeed the case.

With this new oxidation procedure in hand we were able to transform successfully some natural carboxylic acids to the corresponding phosphonic acids (**Table 3**). Oleic acid **1e** and linoleic acid **1f** were chosen as substrates (**Table 3**, Entries 1 and 2) to test the mildness of the new oxidation procedure. Both substrates survived the transformation which is remarkable since linoleic acid is well known to be very sensitive to oxidation. Due to their structures the products were not crystalline but only minor adjustments to the work-up were required.

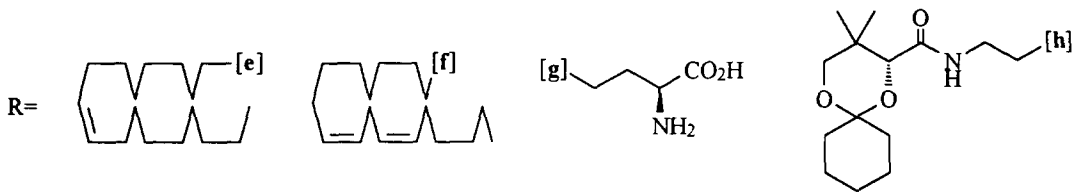
Table 3. Phosphonic acids from natural products

Entry	Starting Material	Product (% yield)
1	2e	3e (80)[a]
2	2f	3f (82)[a]
3	2g	3g (58)[b]
4	2h	3h (50)

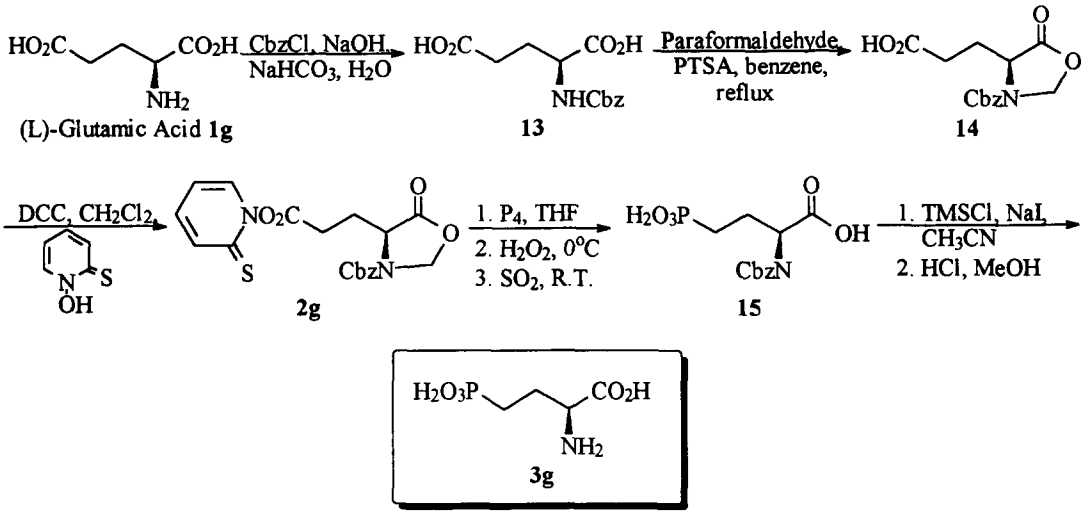
[a] Yield relative to carboxylic acid **1**; [b] yield relative to **13**.



1 **2** **3**



Amino acids having phosphonic acid functional groups are presently of great interest because of their potential biological activity. This interest has spurred many syntheses[3a,3d,11] of phosphonoamino acids including our own. We chose to synthesize (L)-2-amino-4-phosphonobutyric acid **3g** because of its considerable interest and expense ($47 per 1 mg from Sigma Chemical!). We envisioned it could easily be obtained from inexpensive (L)-glutamic acid **1g** with our methodology. With the appropriate protecting groups[12] and a procedure for their removal,[13] the synthesis (**Scheme 3**) was successful affording a good yield of the desired phosphonoamino acid **3g** (**Table 3**, Entry 3). Complete purification of the intermediate products obtained from each step in the synthetic sequence between compounds **13** and **3g** was unnecessary, only a simple work-up protocol was required at each step allowing for a convenient overall synthesis.



Scheme 3

Pantothenic acid, an overlooked but widely consumed compound, was chosen for our final example. It is found in many vitamin supplements but is probably neglected in organic synthesis because it is highly unstable and therefore difficult to handle. Fortunately, it can be stabilized by protecting the hydroxyl groups. Using a modification of two published procedures,[14] the hydroxyl groups of pantothenic acid were successfully protected as the cyclohexyl ketal **1h**. Formation of the corresponding Barton ester **2h** was uneventful providing a nicely crystalline product. Reaction of the Barton ester **2h** with P_4 and subsequent oxidation afforded the desired phosphonic acid **3h** in moderate yield (**Table 3**, Entry 4). Due to the sensitivity of the cyclohexyl ketal towards acid, the reaction was buffered during the oxidation. SO_2 in the presence of water is acidic, therefore to prevent the use of an unreasonable amount of buffer, we returned to the refluxing H_2O_2 oxidation procedure. Under these conditions only a moderate amount of buffer is required to prevent decomposition of the product.

Inhibition of the spontaneous oxidation of white phosphorus and tributylphosphine

One of the major problems associated with phosphines is their extreme sensitivity to oxygen. Unless great care is taken, a purchased or synthesized sample of a phosphine will become fully oxidized before being completely used. Owing to their expense and difficulty in preparation, it would be beneficial to find a method to suppress this oxidation. Many compounds (acrylates, acrylamides, styrenes, and the like) sold today contain either stabilizers or inhibitors to prevent polymerization. In a similar fashion, it may be possible to find an additive that will inhibit the oxidation of phosphines.

White phosphorus is probably the ultimate phosphine in that the molecule consists of four phosphorus atoms, each of which is bonded to three other phosphorus atoms. As such, it is expected to be extremely

reactive towards dioxygen. In fact, on exposure to dioxygen, P_4 will spontaneously combust and it is therefore stored in water.[15] White phosphorus is exceedingly pyrophoric and is difficult to extinguish once it begins to burn.[15] Phosphorus burns heal very slowly, often with scarring.[15] For safety considerations it would be desirable to diminish this reactivity towards dioxygen.

We were impressed with the remarkable inhibitory effect of TEMPO on the reaction between Barton esters and white phosphorus. We conceived that if the oxidation of white phosphorus with dioxygen proceeded through a radical chain process, then the addition of small amounts of TEMPO would prevent the spontaneous oxidation, thus making white phosphorus safer to handle. It seemed the most convenient method for monitoring the effect of TEMPO on the reaction between white phosphorus and dioxygen would be to measure oxygen consumption. With this technique, the amount of dioxygen consumed could be measured as well as the effect of TEMPO on the oxidation.

TEMPO exceeded expectations as an inhibitor, only 0.00025 equivalents (with respect to P_4) were required to produce a 225 minute induction period (**Figure 2**). The impressive induction period was followed by a rapid uptake of oxygen corresponding to three oxygen atoms per phosphorus atom. The results indicated that the reaction of P_4 with dioxygen involves a radical chain process. From the data collected, the radical chain length of P_4 oxidation was estimated to be approximately 13,000. Galvanoxyl **16** and nitrone **17**, both well known radical reaction inhibitors, were also examined, but **16** and **17** were not nearly as effective as TEMPO (**Figure 2**). Although there was not a noticeable induction period, these inhibitors retarded the oxidation of P_4 relative to the control.

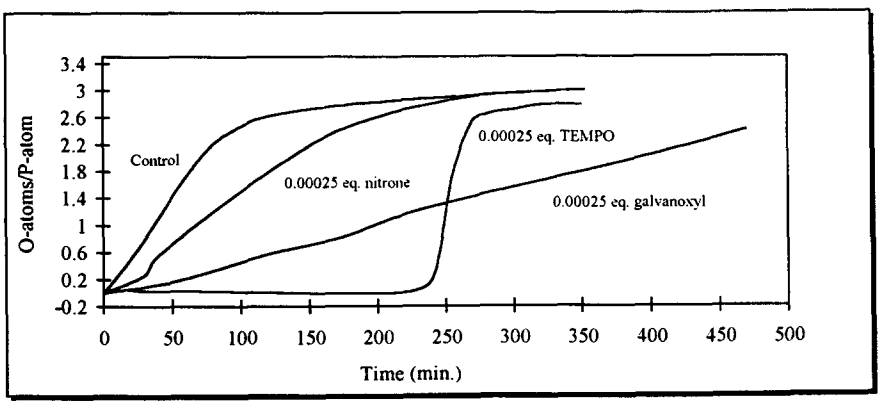
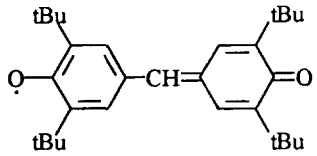
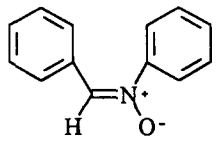


Figure 2. The effect of TEMPO, galvanoxyl, and a nitrone on the oxidation of P_4



Galvanoxyl
16



"Nitrone"
17

We deemed it imperative to determine the generality of TEMPO as an inhibitor of phosphine oxidation. Tri-*n*-butylphosphine was chosen because of its preponderance in modern synthetic laboratories. In this study, as little as 0.0001 equivalents of TEMPO effected an induction period so long (estimated to be between 10 and 22 hours), the oxidation was not followed to conclusion. Although these results were impressive, it was decided that at least one more example was necessary to convincingly show the remarkable inhibitory effect of TEMPO on the oxidation of phosphines.

Since the previous examples involved tertiary phosphines, it was appropriate for the secondary diphenyl phosphine to be tested. Two reactions, using 0.0002 and 0.0004 equivalents of TEMPO, were examined. In both cases there was a rapid uptake of one atom of oxygen followed by an induction period and then a slow uptake of another atom of oxygen. TEMPO did not appear to be an effective inhibitor of the oxidation of secondary phosphines. It was assumed that TEMPO would not effectively inhibit the oxidation of primary phosphines and the study was discontinued.

EXPERIMENTAL SECTION

Materials and instrumentation. The *N*-hydroxy-2-thiopyridone sodium salt was kindly provided by the Olin Corporation. All other chemicals were purchased from Aldrich Chemical. Solvents were used as purchased or dried and purified by standard methods.[16] Melting points were determined with a Bristoline melting point apparatus and were uncorrected. ^{1}H (referenced to TMS at δ 0.00 in $CDCl_3$ unless otherwise stated), ^{13}C (referenced to $CDCl_3$ at δ 77.00), and ^{31}P (referenced to external 85% H_3PO_4 at δ 0.00) NMR spectra were measured at ambient temperature on a Varian XL-200 or a Varian 200 BB spectrometer operating at 200, 50, or 81 MHz respectively, using 5-mm or 10-mm tubes. ^{1}H and ^{13}C spectral data are presented as follows: multiplicity(s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, J = coupling constant, integration). High resolution mass spectra were recorded on a VG Analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer. High resolution FAB spectra were obtained with a 10 KeV Xe beam at 2 mA (primary beam). Microanalyses were performed by Atlantic Microlab Inc., Norcross, GA. All chromatographic separations were performed with silica gel obtained

from Baxter Scientific Products; 60 Å, 230-400 mesh. Irradiations were carried out with a 100 W xenon Q-Beam® 1 million candle power lamp (The Brinkman Corporation, 4215 McEwen Rd., Dallas, Texas 75244).

Preparation and handling of white phosphorus. The white phosphorus was cut and manipulated under water. The oxide coating was removed by sonication in CH_2Cl_2. The phosphorus was weighed into a beaker that contained water. The weighed phosphorus was rinsed with acetone and quickly dabbed dry with a paper towel before it was placed into the reaction solvent.

Determination of dioxygen as the initiator. P_4 (119 mg, 0.96 mmol) was dissolved, under argon, in dry, degassed THF (10 mL), which was gently heated to 50°C until the P_4 had dissolved and then was returned to room temperature. TEMPO (0.037 mg, 0.00024 mmol) was added to the P_4 solution. The phenethyl PTOC ester **2a** (250 mg, 0.96 mmol) was placed in another flask and was flushed with argon. The P_4 solution was added, with a canula, to the flask containing the PTOC ester. The mixture was stirred and aliquots (0.2 mL) were removed (every hour) from the reaction mixture and were quenched with *n*-butyl amine (50 μL). The aliquots were collected and analyzed by TLC until the start of the reaction was evident. This procedure was repeated except that, after the addition of the P_4 solution to the PTOC ester, the reaction was exposed to air.

Rate of the PTOC ester/P_4 reaction without TEMPO. P_4 (47 mg, 0.38 mmol) was dissolved, under argon, in dry, degassed THF (2 mL), which was gently heated to 50°C until the P_4 had dissolved and then was returned to room temperature. Phenethyl PTOC ester **2a** (100 mg, 0.38 mmol) was dissolved in THF (2 mL) that was taken directly from the bottle. The PTOC ester solution was taken up into a syringe and was injected into the P_4 solution. After 30 seconds, *n*-butyl amine (189 μL) was injected into the reaction mixture. This procedure was repeated for reactions that were quenched at 60, 90, and 120 seconds. The quenched reactions were analyzed by TLC to find the end of the reaction.

*Stoichiometry of the reaction between PTOC ester **2a** and P_4.* P_4 (1 mmol) was dissolved, under argon, in dry, degassed THF (enough to make solution 0.1 M with respect to PTOC ester), which was gently heated to 50°C until the P_4 had dissolved and then was returned to room temperature. 2-Phenethyl PTOC ester **1a** (0.5 mmol) was added to the solution and was stirred for 30 minutes. The reaction mixture was treated with 30% H_2O_2 (1 mL/ 100 mg of P_4) and was then refluxed for twelve hours. After the addition of an internal standard (phenylphosphonic acid), the amount of product was determined by ^{31}P-NMR. This procedure was repeated with 1, 1.5, 2, 2.5 mmol of PTOC ester.

General procedures for PTOC ester synthesis[17]

These procedures are suitable for those compounds that give solid PTOC esters of moderate polarity.

From carboxylic acids. DCC (1.05 mmol) and *N*-hydroxy-2-thiopyridone (1.05 mmol) were dissolved in dry CH_2Cl_2 (4 mL). The solution was shielded from light by wrapping the flask with aluminum foil. The carboxylic acid (1 mmol) was dissolved in dry CH_2Cl_2 (4 mL) and added dropwise to the above solution at room temperature. The reaction was stirred for another 90 minutes after the addition had been completed. The reaction mixture was filtered through a short pad of silica gel. CH_2Cl_2 was used to wash the PTOC ester from the silica gel. The CH_2Cl_2 was evaporated under reduced pressure at no higher than 30°C. The residue was recrystallized from CH_2Cl_2/hexanes. PTOC esters are yellow in color and are stored refrigerated and protected from light.

From acid chlorides. Et_3N (1.05 mmol) and *N*-hydroxy-2-thiopyridone (1.05 mmol) were dissolved in dry CH_2Cl_2 (4 mL). This solution was shielded from light by wrapping the flask with aluminum foil. The carboxylic acid chloride (1 mmol) was dissolved in dry CH_2Cl_2 (4 mL) and added dropwise to the above solution at room temperature. The reaction was stirred for another 90 minutes after the addition had been completed. The reaction mixture was either filtered through a short pad of silica gel or simply washed with water and dried over anhydrous $MgSO_4$. CH_2Cl_2 was used to wash the PTOC ester from the silica gel. The CH_2Cl_2 was evaporated under reduced pressure at no higher than 30°C. The residue was recrystallized from CH_2Cl_2/hexanes.

General procedure for phosphonic acid synthesis. P_4 (1 mmol) was dissolved (heat solvent to 45-50°C to facilitate dissolution then cool to room temperature) in dry THF (10 mL), which was distilled under N_2 in order to exclude dissolved O_2. The P_4 solution was prepared under an argon atmosphere. The PTOC ester (1 mmol) was added in one portion to the P_4 solution and the resulting mixture was stirred for 30 minutes at room temperature. The THF was evaporated under reduced pressure and replaced with DME (1,2-dimethoxyethane). The mixture was cooled to 0°C. Catalytic I_2 (optional) was added to the reaction mixture followed by the dropwise addition of 30% H_2O_2 (1 mL/100 mg of P_4). As this oxidation is very exothermic, the peroxide is added slowly. The resulting solution was then refluxed for 12 hours. The DME was evaporated leaving an aqueous **residue** that was not evaporated to dryness, since the presence of residual peroxides may cause a violent explosion.

For compounds with sensitive functional groups an alternative oxidation procedure was utilized: The reaction mixture was cooled to 0°C (replacement of the THF was not necessary) followed by the dropwise addition of 30% H_2O_2 (1 mL/100 mg of P_4). As this oxidation is very exothermic, the peroxide is added slowly. The resulting solution was stirred at room temperature for 15 minutes. SO_2 (270 μL, 6 mmol) was condensed

into a pressure flask at -78°C and the reaction mixture was added dropwise. Since the addition is violent, the reaction mixture is added very slowly. The solution was stirred for 12 hours at room temperature. The THF was evaporated under reduced pressure leaving an aqueous **residue**. As the THF is being evaporated, a white solid may precipitate. This solid is P_4 and should be removed by filtration. A white, mercury-like liquid may oil out. This is also P_4. The P_4 will solidify upon cooling the mixture to 0°C and then can be removed by filtration. Due care should be exercised since P_4 will spontaneously combust upon exposure to oxygen.

The **residue** (from either oxidation procedure) was taken up in EtOAc (20 mL) and washed with an aqueous solution (5 mL) containing conc. H_2SO_4, H_2O, 30% H_2O_2, and brine in a 0.5:1.5:1:7 ratio. The aqueous wash was extracted once with EtOAc (10 mL). The EtOAc extracts were combined and washed with brine (2 x 5 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure.

N-(2-phenylethanoyloxy)pyridine-2(1H)-thione (phenethyl PTOC ester) (2a). The title compound was obtained from dihydrocinnamic acid (10 g) using the general procedure for PTOC ester synthesis. **2a** (11.4 g, 74% recrystallized) was obtained as a yellow, crystalline solid. m.p. 130-132°C dec. (lit.[18]: 135°C dec.). ^{1}H NMR ($CDCl_3$): δ 7.66 (dd, 1H), 7.45-7.11 (m, 7H), 6.74-6.54 (m, 1H), 3.20-2.95 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 175.6, 168.1, 139.1, 137.5, 137.1, 133.6, 128.6, 128.3, 126.6, 112.6, 33.2, 30.2.

2-Phenylethyl-1-phosphonic acid (3a). The title compound was obtained from phenethyl PTOC ester **2a** (1 g) using the general procedure for phosphonic acid synthesis. **3a** (687 mg, 96% unrecrystallized; 58% recrystallized from EtOAc/hexanes) was obtained as a white, crystalline solid. m.p. 133-134°C (EtOAc/hexanes) (lit.[5]: 137-138°C). ^{1}H NMR (DMSO-d_6): δ 9.0-8.65 (s, 2H), 7.4-7.1 (m, 5H), 2.9-2.7 (m, 2H), 1.93-1.70 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 141.8 (d, J_{CP} = 18 Hz), 128.5, 127.9, 126.0, 29.9 (d, J_{CP} = 98 Hz), 28.5 (d, J_{CP} = 33 Hz). ^{31}P NMR (DMSO-d_6): δ 26.7; (acetone-d_6): δ 31.7.

N-(cyclohexanoyloxy)pyridine-2(1H)-thione (cyclohexyl PTOC ester) (2b). The title compound was obtained from cyclohexyl carboxylic acid (6.4 g) using the general procedure for PTOC ester synthesis. **2b** (10.7 g, 91% unrecrystallized) was obtained as a yellow, crystalline solid. m.p. 110-112°C dec. (lit.[18]: 110°C dec.). ^{1}H NMR ($CDCl_3$): δ 7.65 (dd, 1H), 7.58 (dd, 1H), 7.21 (t, 1H), 6.65 (dt, 1H), 2.75 (dt, 1H), 2.35-1.20 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 175.5, 170.9, 137.6, 137.1, 133.4, 112.5, 40.8, 28.5, 25.2, 24.9.

Cyclohexylphosphonic acid (3b). The title compound was obtained from cyclohexyl PTOC ester **2b** (1 g) using the general procedure for phosphonic acid synthesis. **3b** (453 mg, 65% recrystallized from H_2O) was obtained as a white, crystalline solid. m.p. 165-167°C (H_2O) (lit.[6]: 167-168°C). ^{1}H NMR (DMSO-d_6): δ 7.2-6.6 (d,

2H), 2.0-1.0 (m, 11H). ^{13}C NMR (DMSO-d_6): δ 36.2 (d, J_{CP} = 140 Hz), 25.9 (d, J_{CP} = 2 Hz), 25.8 (d, J_{CP} = 22 Hz), 25.7. ^{31}P NMR (DMSO-d_6): δ 29.7.

N-(1-adamantanoyloxy)pyridine-2(1H)-thione (adamantyl PTOC ester) (2c). The title compound was obtained from 1-adamantyl carboxylic acid (1.0 g) using the general procedure for PTOC ester synthesis. **2c** (1.12 g, 75% recrystallized) was obtained as a yellow, crystalline solid. m.p. 164-165°C dec. (lit.[19]: 166°C dec.). ^1H NMR ($CDCl_3$): δ 7.65 (dd, 1H), 7.51 (dd, 1H), 7.26-7.12 (dt, 1H), 6.70-6.57 (dt, 1H), 2.20-2.05 (m, 9H), 1.78 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 175.7, 172.5, 137.7, 137.3, 133.3, 112.5, 40.8, 38.4, 36.0, 27.5.

1-Adamantylphosphonic acid (3c). The title compound was obtained from adamantyl PTOC ester **2c** (508 mg) using the general procedure for phosphonic acid synthesis. **3c** (366 mg, 96% unrecrystallized) was obtained as a white, crystalline solid. m.p. 297-300°C dec. (lit.[7]: 308-310°C dec.). ^1H NMR (DMSO-d_6): δ 8.2-7.7 (s, 2H), 2.0-1.5 (m, 15H). ^{13}C NMR (DMSO-d_6): δ 36.4, 35.4 (d, J_{CP} = 3.4 Hz), 32.9 (d, J_{CP} = 146 Hz), 26.7 (d, J_{CP} = 12 Hz). ^{31}P NMR (DMSO-d_6): δ 30.7.

N-(2,2-dimethylpropanoyloxy)pyridine-2(1H)-thione (pivalic acid PTOC ester).[20] The title compound was obtained from pivalic acid (10.1 g) using the general procedure for PTOC ester synthesis. The PTOC ester (18.7 g, 89% unrecrystallized) was obtained as a yellow, crystalline solid. m.p. 85-90°C. ^1H NMR ($CDCl_3$): δ 7.42 (dd, 1H), 6.68 (dd, 1H), 6.25 (dt, 1H), 5.67 (dt, 1H), 1.3 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 176.0, 173.5, 137.7, 137.5, 133.5, 112.7, 38.9, 27.2.

Ethyl (2-thiopyridyl-4,4-dimethyl)pentanoate. The pivalic acid PTOC ester (5 g, 23 mmol) and the ethyl acrylate (7.1 g, 71 mmol) were dissolved in dry CH_2Cl_2 (80 mL), which was distilled under N_2 in order to exclude dissolved O_2. The solution was prepared under an argon atmosphere and cooled to 0°C. The stirred solution was irradiated with a high powered lamp (white light) until complete by TLC. The CH_2Cl_2 and the excess ethyl acrylate were evaporated under reduced pressure and the product isolated by column chromatography over silica gel (4:1 hexanes/EtOAc). The title compound (4.31 g, 68%) was obtained as a yellow liquid. ^1H NMR ($CDCl_3$): δ 8.42 (d, 1H), 7.49 (t, 1H), 7.20 (d, 1H), 7.00 (t, 1H), 4.61-4.54 (m, 1H), 4.15 (q, 2H), 2.19-2.06 (m, 2H), 1.75-1.65 (m, 2H), 1.22 (t, 3H), 1.00 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.4, 157.4, 149.4, 136.0, 122.4, 119.9, 61.2, 46.0, 43.2, 31.4, 29.4, 14.0. HRMS(FAB): calcd. for $C_{14}H_{21}NO_2S$ ($M+H^+$) 268.1371, found 268.1377.

Ethyl (4,4-dimethyl)pentanoate.[21] Ethyl-(2-thiopyridyl-4,4-dimethyl)pentanoate (4 g, 15 mmol) was dissolved in acetic acid (50 mL). Zinc powder (9.8 g, 150 mmol) was added and the disappearance of starting material

was monitored by TLC. The zinc was filtered off and washed with Et_2O. The filtrate was washed with water (4 x 25 mL) and then with saturated aqueous $NaHCO_3$ (3 x 25 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by column chromatography over silica gel (4:1 hexanes/Et_2O). The title compound (2.08 g, 88%) was obtained as a colorless liquid. ^1H NMR ($CDCl_3$): δ 4.11 (q, 2H), 2.32-2.16 (m, 2H), 1.62-1.49 (m, 2H), 1.26 (t, 3H), 0.9 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.5, 60.2, 38.6, 30.2, 30.1, 29.0, 14.2.

4,4-Dimethylpentanoic acid (1d).[22] Ethyl-(4,4-dimethyl)pentanoate (2 g, 12 mmol) was dissolved in THF (25 mL). LiOH (864 mg, 36 mmol) was dissolved in water (25 mL) and added to the above solution. The mixture was stirred vigorously while being refluxed. The reaction was allowed to continue for 7 hours. The THF was evaporated under reduced pressure leaving an aqueous solution. The aqueous solution was washed with Et_2O (3 x 20 mL), acidified with aqueous HCl, and then extracted with EtOAc. The EtOAc extracts were combined, dried with anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. **1d** (1.55 g, 95%) was obtained as a colorless liquid. ^1H NMR ($CDCl_3$): δ 2.38-2.28 (m, 2H), 1.62-1.51 (m, 2H), 0.91 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 181.3, 38.3, 30.0, 29.9, 28.9.

N-(4,4-dimethlypentanoyloxy)pyridine-2(1H)-thione (t-butylethyl PTOC ester) (2d). The title compound was obtained from the acid **1d** (1.55 g) using the general procedure for PTOC ester synthesis. The PTOC ester **2d** (2.6 g, 91%) was obtained as a yellow, crystalline solid. m.p. 102-105 °C dec. (Et_2O/hexanes). ^1H NMR ($CDCl_3$): δ 7.69 (d, 1H), 7.58 (d, 1H), 7.21 (t, 1H), 6.65 (t, 1H), 2.75-2.64 (m, 2H), 1.80-1.67 (m, 2H), 0.94 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 175.8, 169.6, 137.6, 137.3, 133.5, 112.6, 37.7, 30.1, 28.9, 27.5. Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found C, 60.07; H, 7.09; N, 5.81.

3,3-Dimethylbutyl-1-phosphonic acid (3d). The title compound was obtained from the PTOC ester **2d** (2.5 g) using the general procedure for phosphonic acid synthesis. **3d** (1.4 g, 80 %) was obtained as a white, crystalline solid. m.p. 190°C (H_2O). ^1H NMR (DMSO-d_6): δ 9.04 (s, 2H), 1.55-1.25 (m, 4H), 0.83 (s, 9H). ^{13}C NMR (DMSO-d_6): δ 36.4 (d, J_{CP} = 4 Hz), 30.0 (d, J_{CP} = 17 Hz), 28.8, 22.9 (d, J_{CP} = 137 Hz). ^{31}P NMR (DMSO-d_6): δ 31.0. Anal. Calcd. for $C_6H_{15}O_3P$: C, 43.37; H, 9.10. Found C, 43.54; H, 9.09.

N-(9-octadecenoyloxy)pyridine-2(1H)-thione (oleic PTOC ester) (2e).[18] DCC (3.82 g, 18.6 mmol) and *N*-hydroxy-2-thiopyridone (2.36 g, 18.6 mmol) were dissolved in dry CH_2Cl_2 (70 mL). This solution was shielded from light by wrapping the flask with aluminum foil. Oleic acid **1e** (4.77g, 16.9 mmol) was dissolved in dry CH_2Cl_2 (70 mL) and added dropwise to the above solution at room temperature. The reaction was stirred for another 90 minutes after the addition had been completed. The CH_2Cl_2 was evaporated under reduced pressure

at no higher than 30°C. The residue was taken up in Et_2O (50 mL) and the solid was removed by filtration. The solution was washed with 5% $NaHCO_3$ (3 x 10 mL), dried with anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure at no higher than 30°C. The PTOC ester **2e** (5.9 g, 90%) was obtained as a yellow oil. All manipulations of the PTOC ester were performed in a dimly lit room. **2e** was stored at -20°C. ^1H NMR ($CDCl_3$): δ 7.4 (d, 1H), 6.7 (d, 1H), 6.2 (t, 1H), 5.6 (t, 1H), 5.45 (m, 2H), 2.5-0.8 (m, 31H). ^{13}C NMR ($CDCl_3$): δ 175.8, 169.0, 137.6, 137.3, 133.5, 130.0, 129.6, 112.5, 31.8, 31.5, 29.7, 29.6, 29.5, 29.3, 29.0, 28.9, 27.2, 27.1, 24.2, 22.6, 14.1.

8-Heptadecene-1-phosphonic acid (3e). P_4 (644 mg, 5.2 mmol) was dissolved (heat solvent to 45-50°C to facilitate dissolution then cool to room temperature) in dry THF (40 mL), which was distilled under N_2 in order to exclude dissolved O_2. The PTOC ester **2e** (1.91 g, 4.8 mmol) was also dissolved in dry, deoxygenated THF (10 mL) and then placed in a dropping funnel. The PTOC ester solution was added in one portion to the P_4 solution and the resulting mixture was stirred for 30 minutes at room temperature. Both solutions were prepared under an argon atmosphere. The reaction mixture was cooled to 0°C and 30% H_2O_2 (6 mL) was added dropwise. As this oxidation is very exothermic, the peroxide was added slowly. The resulting solution was stirred at room temperature for 15 minutes. SO_2 (~2 mL) was condensed into a pressure flask at -78°C and the reaction mixture was added dropwise. Since the addition is violent, the reaction mixture was added very slowly. The solution was stirred for 12 hours at room temperature. The THF was evaporated under reduced pressure leaving an aqueous residue. As the THF is being evaporated a white solid may precipitate. This solid is P_4 and should be removed by filtration. A white, mercury-like liquid may oil out. This is also P_4. The P_4 will solidify upon cooling the mixture to 0°C and then can be removed by filtration. Due care should be exercised since P_4 may spontaneously combust upon exposure to oxygen. The residue was taken up in EtOAc (20 mL), washed with an aqueous solution (10 mL) containing conc. H_2SO_4, H_2O, 30% H_2O_2, and brine in a 0.5:1.5:1:7 ratio, and then washed with brine (2 x 10 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was taken up in MeOH (50 mL) and treated with $LiOH{\cdot}H_2O$ (410 mg). The mixture was stirred for 30 minutes and then centrifuged. The MeOH was discarded and the solid taken up in EtOAc (20 mL). The mixture was centrifuged and the EtOAc discarded. This step was repeated until the EtOAc was clean (no high running spots) by TLC. EtOAc was used as the eluent and u.v., I_2, and $PdCl_2$ were used as the indicators for the TLC analysis. The solid can also be obtained by filtration, albeit rather slowly. The solid thus obtained was suspended in EtOAc (30 mL) and treated with a solution (20 mL) containing conc. H_2SO_4, H_2O, and brine in a 0.5:1.5:8 ratio. The layers were separated and the EtOAc was washed with brine (10 mL), dried with anhydrous $MgSO_4$, and evaporated under reduced pressure. Traces of EtOAc were removed by multiple freeze-thawing with liquid N_2 under vacuum. The phosphonic acid **3e** (1.23 g, 80%) was obtained as a waxy, white solid. m.p. 50-60°C. ^1H NMR ($CDCl_3$):

δ 5.4 (m, 2H), 2.2-0.9 (m, 31H). ^{13}C NMR ($CDCl_3$): δ 130.0, 129.7, 31.9, 29.8, 29.7, 29.5, 29.3, 29.1, 27.2, 27.1, 22.7, 14.1. ^{31}P NMR ($CDCl_3$): δ 36.9. HRMS(FAB): calcd. for $C_{17}H_{35}O_3P$ ($M + Na^+$) 341.2221, found 341.2211.

N-(9,12-octadecadienoyloxy)pyridine-2(1H)-thione (linoleic PTOC ester) (2f).[18] The title compound was obtained from linoleic acid **1f** (1 g) utilizing the procedure described for the synthesis of the oleic PTOC ester **2e**. The product (1.25 g, 90%) was obtained as a yellow oil. **2f** was stored at -20°C under an inert atmosphere. ^{1}H NMR ($CDCl_3$): δ 7.7 (d, 1H), 7.58 (d, 1H), 7.25 (t, 1H), 6.65 (t, 1H), 5.5-5.3 (m, 4H), 2.8-0.9 (m, 29H). ^{13}C NMR ($CDCl_3$): δ 175.9, 169.1, 137.7, 137.4, 133.6, 130.3, 130.0, 128.2, 128.0, 112.6, 31.6, 31.5, 29.6, 29.4, 29.1, 29.0, 27.2, 27.1, 25.7, 24.3, 22.6, 14.1.

8,11-Heptadecadiene-1-phosphonic acid (3f). The title compound was obtained from linoleic PTOC ester **2f** (1.25 g) utilizing the procedure described for the synthesis of 8-heptadecene-1-phosphonic acid **3e**. The phosphonic acid **3f** (913 mg, 82% yield from linoleic acid) was obtained as a light yellow oil. **3f** was stored at -20°C under an inert atmosphere. ^{1}H NMR ($CDCl_3$): δ 5.35 (m, 4H), 2.9-0.8 (m, 29H). ^{13}C NMR ($CDCl_3$): δ 130.2, 129.9, 128.0, 127.8, 31.5, 29.6, 29.3, 29.1, 27.2, 25.6, 22.6, 14.1. ^{31}P NMR ($CDCl_3$): δ 36.9. HRMS(FAB): calcd. for $C_{17}H_{33}O_3P$ ($M + Na^+$) 339.2065, found 339.2083.

(S)-N-(3-benzoyloxycarbonyl-5-oxo-4-oxazolidinepropanoyloxy)pyridine-2(1H)-thione (2g).[23] DCC (3.7 g, 18.0 mmol) and *N*-hydroxy-2-thiopyridone (2.3 g, 18.0 mmol) were dissolved in dry CH_2Cl_2 (70 mL). This solution was shielded from light by wrapping the flask with aluminum foil. (S)-3-benzoyloxycarbonyl-5-oxo-4-oxazolidinepropionic acid[12] **14** (5.0 g, 17.0 mmol) was dissolved in dry CH_2Cl_2 (70 mL) and added dropwise to the above solution at room temperature. The reaction was stirred for another 90 minutes after the addition had been completed. The reaction mixture was stirred at -78°C for one hour (or stored at -20°C over night) and the solid was removed by filtration. The solution was washed with 5% $NaHCO_3$ (2 x 50 mL), dried with anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure at no higher than 30°C. All manipulations of the PTOC ester were performed in a dimly lit room. The PTOC ester **2g** (6.17 g, 90%) was obtained as a yellow oil and was stored at -20°C. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 1H), 7.40-7.20 (m, 6H), 7.18 (t, 1H), 6.60 (t, 1H), 5.50 (d, 1H), 5.25 (d, 1H), 5.18 (s, 2H), 4.40 (t, 1H), 2.85 (t, 2H), 2.50-2.20 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 174.7, 171.2, 167.5, 152.6, 137.4, 136.2, 134.8, 133.6, 128.1, 128.0, 127.6, 112.5, 77.4, 77.2, 67.5, 53.1, 26.7, 24.9.

(S)-N-benzoyloxycarbonyl-2-amino-4-phosphonobutyric acid (15).[11c] P_4 (1.8 g, 14.5 mmol) was dissolved (heat solvent to 45-50°C to facilitate dissolution then cool to room temperature) in dry THF (100 mL), which

was distilled under N_2 in order to exclude dissolved O_2. The PTOC ester **2g** (5.8 g, 14.5 mmol) was also dissolved in dry, deoxygenated THF (45 mL) and then placed into a dropping funnel. The PTOC ester solution was added in one portion to the P_4 solution and the resulting mixture was stirred for 30 minutes at room temperature. Both solutions were prepared under an argon atmosphere. The reaction mixture was cooled to 0°C and 30% H_2O_2 (18 mL) was added dropwise. As this oxidation is very exothermic, the peroxide was added slowly. The resulting solution was stirred at room temperature for 15 minutes. SO_2 (5-10 mL) was condensed into a pressure flask at -78°C and the reaction mixture was added dropwise. Since the addition is violent, the reaction mixture was added very slowly. The solution was stirred for 12 hours at room temperature. The THF was evaporated under reduced pressure leaving an aqueous residue. As the THF is being evaporated, a white solid may precipitate. This solid is P_4 and should be removed by filtration. A white, mercury-like liquid may oil out. This is also P_4. The P_4 will solidify upon cooling the mixture to 0°C and then can be removed by filtration. Due care should be exercised since P_4 will spontaneously combust upon exposure to oxygen. The residue was taken up in EtOAc (80 mL) and washed with an aqueous solution (10 mL) containing conc. H_2SO_4, H_2O, 30% H_2O_2, and brine in a 0.5:1.5:1:7 ratio. The aqueous wash was extracted once with EtOAc (10 mL). The EtOAc extracts were combined and washed with brine (2 x 10 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The phosphonic acid **15** (4.2 g, 92%) was obtained as a colorless oil. Although sufficiently pure for preparative purposes, the phosphonic acid was treated with diazomethane and further purified by column chromatography to obtain a pure sample. ^{1}H NMR ($CDCl_3$): δ 7.40-7.30 (m, 5H), 6.01 (d, 1H), 5.10 (s, 2H), 4.45-4.30 (m, 1H), 3.75-3.60 (m, 9H), 2.30-1.70 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 171.8, 155.9, 136.0, 128.3, 127.9, 127.8, 66.8, 53.7 (d, J_{CP} = 18 Hz), 52.3, 52.2, 25.2 (d, J_{CP} = 4 Hz), 20.6 (d, J_{CP} = 143 Hz). ^{31}P NMR ($CDCl_3$): δ 33.5.

(L)-2-amino-4-phosphonobutyric acid (3g). The phosphonic acid **15** (4.2 g; 13.2 mmol) was dissolved in dry CH_3CN (30 mL) and treated with Me_3SiCl (6.7 mL, 52.8 mmol) and NaI (7.8 g, 52.8 mmol). The reaction was stirred for one hour at room temperature. The solid was removed by filtration and the mother liquor was treated with a saturated solution (12 mL) of HCl in MeOH. The mixture was stirred for one hour at room temperature after which propylene oxide (10 mL) was added. The reaction mixture was stirred for another 30 minutes. The white solid (2.95 g) was collected by filtration giving the desired, fully deprotected amino acid **3g**. The solid (mixture of amino acid and HCl salt) was dissolved in water and refluxed to drive off the HCl. The water was evaporated leaving an aqueous residue which was taken up in MeOH. **3g** precipitated as a white solid upon addition of the MeOH. The solid (1.9 g, 58% from **13**) was filtered and washed with cold MeOH. m.p. 206-208 °C (aq. EtOH) (lit.[24] 205-207°C (aq. EtOH)). $[\alpha]_D^{25}$ +10.3 (c=2, H_2O) (lit.[24] $[\alpha]_D^{25}$ +11.2 (c=2, H_2O)). ^{1}H NMR (D_2O): δ 3.70 (t, 1H), 2.05-1.85 (m, 2H), 1.70-1.35 (m, 2H). ^{13}C NMR (D_2O): δ 173.5, 54.7 (d, J_{CP} = 16 Hz), 25.0 (d, J_{CP} = 3 Hz), 23.9 (d, J_{CP} = 134 Hz). ^{31}P NMR (D_2O): δ 24.2.

Pantothenic acid cyclohexyl ketal (1h).[14] $(EtO)_3CH$ (9.1 mL, 55 mmol) was added dropwise to a mixture of cyclohexanone (5 g, 10.5 mmol), concentrated H_2SO_4 (64 μL, 0.636 mmol), and 3 Å molecular sieves. The mixture was heated at 100 °C for 15 minutes and was then cooled to 0°C. Calcium pantothenoate (5 g, 10.5 mmol) and 3 Å molecular sieves were suspended in dioxane (35 mL) at 0°C. The suspension was treated with concentrated H_2SO_4 followed by the addition (by canula) of the reaction mixture prepared previously. The stirred reaction mixture was allowed to warm to room temperature overnight. The solid was removed by filtration and the filtrate treated with 5% $NaHCO_3$ (100 mL) and washed with EtOAc (3 x 20 mL). The aqueous solution was cooled to 0°C, acidified with HCl, and extracted with EtOAc (3 x 20 mL). The extracts were combined, dried with anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. **1h** (5.87 g, 93% yield) was obtained as a colorless oil. $[\alpha]_D^{25}$ +53.18 (c=4.83, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.19 (t, 1H), 4.18 (s, 1H), 3.74 (d, 1H), 3.55 (m, 2H), 3.25 (d, 1H), 2.60 (t, 2H), 2.00-1.30 (m, 11H), 1.02 (s, 3H), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 176.4, 170.4, 99.2, 76.0, 70.5, 38.1, 34.0, 33.8, 33.1, 27.3, 25.5, 22.6, 22.3, 22.0, 18.9. HRMS(FAB): calcd. for $C_{15}H_{25}NO_5$ ($M+H^+$) 300.1811, found 300.1829.

Pantothenic acid cyclohexyl ketal PTOC ester (2h). The title compound was obtained from pantothenic acid cyclohexyl ketal **1h** (5.6 g) using the general procedure for PTOC ester synthesis. **2h** (5.82 g, 76% recrystallized) was obtained as a yellow, crystalline solid. m.p. 118-120°C dec. (Et_2O). $[\alpha]_D^{25}$ +16.09 (c=4.97, MeOH). ^1H NMR ($CDCl_3$): δ 7.75-7.6 (m, 2H), 7.40 (t, 1H), 7.25 (dt, 1H), 6.65 (dt, 1H), 4.15 (s, 1H), 3.95-3.60 (m, 3H), 3.25 (d, 1H), 2.90 (t, 2H), 2.00-1.30 (m, 11H), 1.05 (s, 3H), 1.02 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 175.6, 170.4, 167.2, 137.5, 137.2, 133.6, 112.6, 99.2, 76.1, 70.6, 38.1, 34.2, 33.2, 32.7, 27.2, 25.4, 22.6, 22.3, 22.1, 19.1. Anal. Calcd. for $C_{20}H_{28}N_2O_5S$: C, 58.80; H, 6.91; N, 6.86. Found C, 58.84; H, 6.96; N, 6.84.

Pantothenic acid cyclohexyl ketal phosphonic acid (3h). P_4 (151 mg, 1.23 mmol) was dissolved in dry THF (10 mL), which was distilled under N_2 in order to exclude dissolved O_2. The PTOC ester **2h** (500 mg, 1.23 mmol) was added in one portion to the P_4 solution and the resulting mixture was stirred for 30 minutes at room temperature. The P_4 solution was prepared under an argon atmosphere. K_2HPO_4 (1.28g, 7.38 mmol) was dissolved in water (4 mL) and added to the reaction mixture. The mixture was cooled to 0°C. Catalytic I_2 (optional) was added to the reaction mixture followed by the dropwise addition of 30% H_2O_2 (1.5 mL). As this oxidation is very exothermic, the peroxide was added slowly. The resulting solution was then refluxed for 12 hours. The addition of H_2O_2 (1.5 mL) followed by 12 hours of refluxing was repeated twice. The THF was evaporated leaving an aqueous residue that was not evaporated to dryness, since the presence of residual peroxides may cause a violent explosion. The aqueous residue was diluted with brine (10 mL) and extracted with EtOAc (3 x 10 mL). The aqueous residue was then cooled to 0°C and acidified with an aqueous solution

(0°C) containing concentrated H_2SO_4, water, and brine in a 0.5:1.5:8 ratio. The acidified residue was extracted with EtOAc (3 x 20 mL). The extracts were combined, dried with anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. **3h** (206 mg, 50%) was obtained as a colorless gum. Although sufficiently pure for preparative purposes, the phosphonic acid was treated with diazomethane and further purified by column chromatography to obtain a pure sample of the dimethyl ester. $[\alpha]_D^{25}$ +50.57 (c=9.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.10 (t, 1H), 4.10 (s, 1H), 3.75 (d, 6H), 3.70 (d, 1H), 3.69-3.45 (m, 2H), 3.25 (d, 1H), 2.15-1.90 (m, 2H), 1.90-1.30 (m, 10H), 1.02 (s, 3H), 1.00 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 169.6, 98.8, 77.2, 75.8, 70.3, 52.1 (d, J_{CP} = 6 Hz), 52.0 (d, J_{CP} = 6 Hz), 37.9, 32.9, 32.3 (d, J_{CP} = 5 Hz), 27.0, 25.2, 24.7 (d, J_{CP} = 140 Hz), 22.3. ^{31}P NMR ($CDCl_3$): δ 32.1. HRMS(FAB): calcd. for $C_{16}H_{30}NO_6P$ ($M+Na^+$) 386.1708, found 386.1716.

The effect of various radical inhibitors on the oxidation of P_4. P_4 (10 mg, 0.08 mmol) was dissolved, under argon, in dry, degassed THF (2 mL), which was gently heated to 50°C until the P_4 had dissolved and then was returned to room temperature. The stirred P_4 solution was then exposed to dioxygen with an apparatus (illustrated below) that measures oxygen consumption. Measurements (volume of O_2) were taken from the apparatus at reasonable intervals (10-15 minutes). Along with each measurement, the temperature and, if possible, the atmospheric pressure were recorded. The volume of O_2 recorded at each time interval was converted to millimoles of O_2 with the equation: PV=nRT [P = pressure (atm); V = volume (L); n = moles; R = gas constant (0.0821 L•atm/(K•mol)); T = temperature (K)].

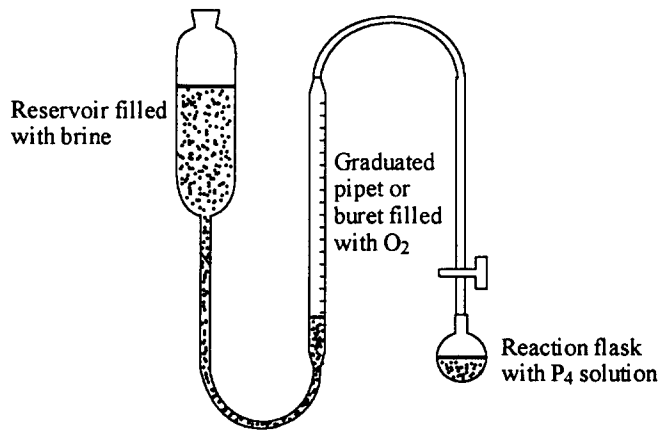


Figure 3. Apparatus for measuring O_2 consumption

The above procedure was repeated for P_4 solutions treated with TEMPO ($2x10^{-5}$ mmol), galvanoxyl **16** ($2x10^{-5}$ mmol), and nitrone **17** ($2x10^{-5}$ mmol).

The effect of TEMPO on the oxidation of Bu_3P. Bu_3P (180 mg, 0.89 mmol) was dissolved, under argon, in dry, degassed THF (5 mL). The solution was treated with TEMPO ($8.9x10^{-5}$ mmol) and then exposed to oxygen with the apparatus illustrated above. Measurements were taken from the apparatus at reasonable intervals (10-15 minutes). Along with each measurement, the temperature and, if possible, the atmospheric pressure were recorded. The volume of O_2 recorded at each time interval was converted to millimoles of O_2 with the equation: PV=nRT [P = pressure (atm); V = volume (L); n = moles; R = gas constant (0.0821 L•atm/(K•mol)); T = temperature (K)].

The effect of TEMPO on the oxidation of Ph_2PH. Ph_2PH (83 mg, 0.44 mmol) was dissolved, under argon, in dry, degassed THF (2 mL). The solution was treated with TEMPO ($8.9x10^{-5}$ mmol) and then exposed to oxygen with the apparatus illustrated above. Measurements were taken from the apparatus at reasonable intervals (10-15 minutes). Along with each measurement, the temperature and, if possible, the atmospheric pressure were recorded. The volume of O_2 recorded at each time interval was converted to millimoles of O_2 with the equation: PV=nRT [P = pressure (atm); V = volume (L); n = moles; R = gas constant (0.0821 L•atm/(K•mol)); T = temperature (K)]. The reaction was repeated with $1.8x10^{-4}$ mmol of TEMPO.

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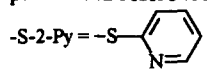
4. -S-2-Py = 
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