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Catalytic Oxidative Ring Opening of THF Promoted by a Carboxylate-Bridged Diiron Complex, Triarylphosphines, and Dioxygen

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The catalytic oxidation of triphenylphosphine in the presence of dioxygen by the diiron(II) complex $[Fe_2(\mu\text{-}O_2CAr^{Tol})_2(Me_3TACN)_2(MeCN)_2](OTf)_2$ (**1**), where $^{-}O_2CAr^{Tol}$ = 2,6-di(*p*-tolyl)benzoate and Me_3TACN = 1,4,7-trimethyl-1,4,7-triazacyclononane, has been investigated. The corresponding diiron(III) complex, $[Fe_2(\mu\text{-}O)(\mu\text{-}O_2CAr^{Tol})_2(Me_3TACN)_2](OTf)_2$ (**2**), the only detectable iron-containing species during the course of the reaction, can itself promote the reaction. Phosphine oxidation is coupled to the catalytic oxidation of THF solvent to afford, selectively, the C–C bond-cleavage product 3-hydroxypropylformate, an unprecedented transformation. After consumption of the phosphine, solvent oxidation continues but results in the products 2-hydroperoxytetrahydrofuran, butyrolactone, and butyrolactol. The similarities of the reaction pathways observed in the presence and absence of catalyst, as well as ^{18}O labeling, solvent dependence, and radical probe experiments, provide evidence that the oxidation is initiated by a metal-centered H-atom abstraction from THF. A mechanism for catalysis is proposed that accounts for the coupled oxidation of the phosphine and the THF ring-opening reaction.

Introduction

Non-heme diiron monooxygenases comprise an important group of dioxygen-activating enzymes capable of oxidizing organic substrates, ranging from functionalized arenes to the compact and highly inert molecule methane. Over the past two decades, much effort has been invested in synthesizing functional small-molecule mimics of these enzymes.[1−3] The soluble form of methane monooxygenase (sMMO) (Figure 1), containing a hydroxylase component (MMOH) which mediates the selective conversion of methane and dioxygen to methanol, has attracted particular interest.[4] Its signature transformation is remarkable from a chemical standpoint, and a selective synthetic catalyst for this reaction would be of both fundamental and practical importance because it would allow more efficient exploitation of natural gas.[5]

We recently reported that a synthetic model for the reduced, diiron(II) form of MMOH, $[Fe_2(\mu\text{-}O_2CAr^{Tol})_2(Me_3TACN)_2(MeCN)_2](OTf)_2$ (**1**, Chart 1), catalyzes the oxidation of triphenylphosphine to its corresponding oxide in the presence of dioxygen.[6] Several thousand turnovers could be achieved by slow addition of the phosphine to the catalyst solution. Early experiments suggested the possibility that the oxidation was occurring by a catalytic mechanism similar to that of MMOH, which would represent an important advance in the modeling of metalloenzymes. The concurrent discovery that the corresponding diiron(III) complex $[Fe_2(\mu\text{-}O)(O_2CAr^{Tol})_2(Me_3TACN)_2](OTf)_2$ (**2**) could function as the catalyst, without any detectable participation of complex **1**, made us wonder whether our putative MMOH mimic might be initiating rather than participating in the catalysis. We report here the results of extensive investigations of this system, which reveal that the THF solvent is a critical component of the catalytic cycle, forming the unusual ring-opened product 3-hydroxypropylformate (**3**, Chart 2). Mechanistic studies of this reaction and the coupled consumption of phosphine are described.

Experimental Section

General Considerations. All reagents were obtained from commercial sources and used without further purification unless

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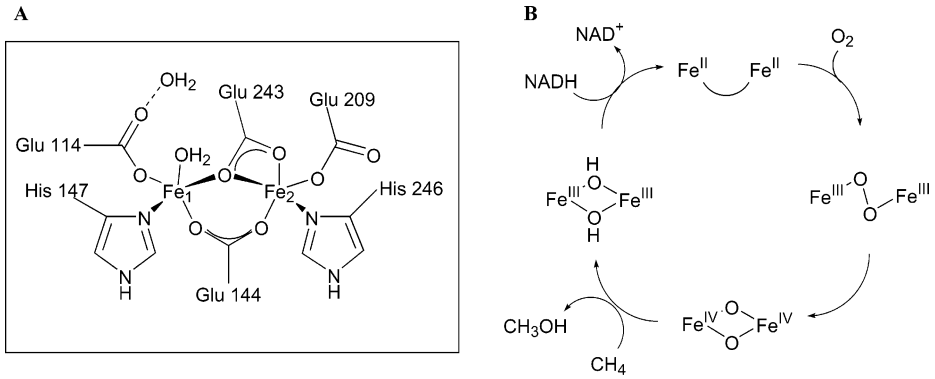
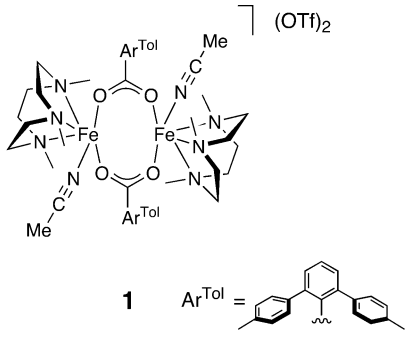


Figure 1. (A) Active site of MMOH in its reduced, diiron(II) form. (B) The catalytic cycle of sMMO as it is presently understood.

Chart 1



1 Ar^{Tol} =

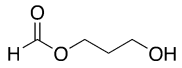
otherwise noted. THF and other solvents were saturated with argon and purified by passage through activated Al_2O_3 columns under an argon atmosphere.[7] Air-sensitive manipulations were carried out under a nitrogen atmosphere. All flasks, pipets, syringes, NMR tubes, and other glassware used in oxidation reactions were thoroughly rinsed with freshly purified THF and dried briefly at 100 °C before use. Complexes **1** and **2** were prepared as previously described.[6]

Physical Measurements. FT-IR spectra were recorded on a Bio-Rad FTS-135 instrument, UV−vis spectra were recorded on a Hewlett-Packard 8453 diode-array spectrophotometer; mass spectra were recorded on an Agilent 1100 Series LC/MSD system; and ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer or an Inova 500 MHz spectrometer. Proton chemical shifts are reported versus tetramethylsilane and calibrated using residual solvent peaks. ^{19}F NMR spectroscopic data were collected on an Inova 500 MHz spectrometer using an external $CFCl_3$ standard. Acquisition parameters were optimized for a 2.0 mM solution of tris(4-fluorophenyl)phosphine (pw(90) = 7.9 μs, d1 = 12.5 s, nt = 2, sw = 9429.5, tof = −2486.6). All spectra were recorded at 20 °C.

Phosphine Oxidation in THF. Catalyst **2** (2.2 mg, 1.6 μmol) was dissolved in 1.0 mL of THF under a nitrogen atmosphere. In a separate vessel, tris(4-fluorophenyl)phosphine (5.1 mg, 16.0 μmol) was dissolved in 6.0 mL of freshly purified, air-saturated THF. To an NMR tube were added 0.6 mL of the phosphine stock solution and 0−450 μL of THF. The catalyst stock solution (50−400 μL) was introduced just before measurement to give a final volume of 0.80 mL, a phosphine concentration of 2.0 mM, and 1.0−10 mol % catalyst relative to phosphine. The reaction was monitored by ^{19}F NMR spectroscopy.

Phosphine Oxidation in Other Solvents. Reactions were performed in a manner similar to that described above but in different solvents. All solvents were purified by distillation or passage through an alumina column under Ar just before use. A control reaction in THF was run in parallel with all experiments. In cases where catalyst solubility was insufficient, a THF solution of the catalyst was first added directly to the NMR tube, after which the solvent was removed with a stream of nitrogen; the phosphine stock solution in the solvent of interest was then added to the tube just before measurement. Slow oxidation (affording ∼50% conversion after 12 h) was observed in diethyl ether and methyl *tert*-butyl ether. No oxidation occurred in toluene, dichloromethane, chloroform, acetone, or acetonitrile.

Chart 2



3

Attempted Reaction of Tris(4-fluorophenyl)phosphine Oxide with $[Fe_2(\mu\text{-}O_2CAr^{Tol})_2(Me_3TACN)_2(MeCN)_2](OTf)_2$ (1). Complex **1** (2.6 mg, 1.9 μmol) was dissolved in 4 mL of THF under N_2. Tris(4-fluorophenyl)phosphine oxide (6.5 mg, 20 μmol) was dissolved in 400 μL of THF, and a 140 μL aliquot (7 μmol, 4 equiv) was added dropwise over several minutes. No color change was observed. After it was stirred overnight, the solution was analyzed by ^{19}F NMR spectroscopy. Only the starting phosphine oxide was detected.

Identification of THF Oxidation Products by ^{1}H NMR Spectroscopy. A representative procedure is given. Complex **2** (2.5 mg, 1.8 μmol) was dissolved in 1.1 mL of THF under N_2. In a separate vessel, a stock solution of tris(4-fluorophenyl)phosphine (2.2 mg, 7.0 μmol) in air-saturated THF (3.5 mL) was prepared. A 0.7 mL aliquot of this solution was added to an NMR tube along with 50 μL of d_6-benzene for locking purposes. Just prior to measurement, 4 μL (0.5 mol %) of the catalyst stock solution was added to the NMR tube and the contents were thoroughly mixed. The reaction was monitored by ^{1}H NMR spectroscopy over a period of 18 h. Identification of 3-hydroxypropylformate (**3**, Chart 2) after detection by ^{1}H NMR spectroscopy in THF (δ 7.8 (s, CHO), 4.1 (t, $-CH_2$)) is discussed below. The products 2-hydroperoxytetrahydrofuran (**4**), butyrolactone (**5**), and butyrolactol (**6**) were identified by comparison to authentic samples.

Autoxidation of Tris(4-fluorophenyl)phosphine and THF in the Absence of Catalyst. A 2.0 mM solution of tris(4-fluorophenylphosphine) in THF was prepared and allowed to stand in air. Aliquots of 0.6 mL were periodically removed, mixed with d_6-benzene (50 μL), and analyzed by ^{1}H NMR spectroscopy. In the dark, this solution remained unchanged over a period of 23 days. When it was subsequently exposed to ordinary room light, slow autoxidation occurred. The evolution of formate **3** and

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phosphine oxide occurred during the first 2 days, and formation of 2-hydroperoxytetrahydrofuran was readily apparent once the phosphine was fully consumed.

Isolation and Identification of 3-Hydroxypropylformate (3). Dioxygen was bubbled through a solution of complex **1** (12 mg, 8.9 μmol) in THF (5.5 mL) at −78 °C for 30 min. After 12 h at −78 °C, N_2 was bubbled through the solution for 15 min, and the vessel was allowed to come to room temperature. The catalyst solution was then added to a solution of tris(4-fluorophenyl)-phosphine (500 mg, 1.60 mmol) in air-saturated THF (∼700 mL), and the mixture was stirred in the air and monitored by TLC until phosphine oxidation was nearly complete. At this point, a second aliquot of (4-fluorophenyl)phosphine (500 mg, 1.60 mmol) was added and stirring was continued until the reaction was near completion. An additional 200 mg of phosphine was added to prevent formation of peroxide-derived products, and the reaction mixture was filtered through silica. The volume of the solution was reduced to about 100 mL. Toluene (∼50 mL) was added, allowing removal of the remaining THF without loss of volatile oxidation products, and the solution was further concentrated. Column chromatography on silica (10−40% ethyl acetate/pentane) afforded formate **3**, which was identified by COSY, HSQC, ^{1}H, and ^{13}C NMR spectroscopy. The assignment was later confirmed by comparison of the NMR, IR, and mass spectra with those of an authentic sample (see below).

Independent Synthesis of 3-Hydroxypropylformate (3). Acetic formic anhydride was prepared by dropwise addition of formic acid to acetic anhydride and heating at 55−60 °C for 2 h.[8] After the reaction was cooled to room temperature, 4.44 g (30 mmol mixed anhydride, assuming quantitative yield) of this solution was added dropwise to a solution of 1,3-propanediol (2.17 mL, 30 mmol) in pyridine (40 mL) at −40 °C. The reaction was stirred at 0 °C for 2 h and allowed to stand overnight at −20 °C. The pyridine and acetic acid were removed by distillation. About 300 mg of the remaining mixture of monoformate, diformate, and unreacted diol was chromatographed on silica (10−40% ethyl acetate/hexanes) to provide 96 mg of the desired monoformate. ^{1}H NMR ($CDCl_3$): δ 8.09 (s, 1H), 4.34 (t, J = 6.1 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 1.92 (m, 2H). ^{13}C NMR: δ 30.59, 58.58, 62.29, 165.14. IR: 3370 (ν_{O-H}), 1723 cm^{-1} ($\nu_{C=O}$). MS (EI): m/z 104 (M^+).

Phosphine Oxidation in the Presence of $^{18}O_2$. Complex **2** (3.4 mg, 0.0025 mmol, 5 mol %) and (4-fluorophenyl)phosphine (15.8 mg, 0.050 mmol) were dissolved in 25 mL of THF under N_2 in a Schlenk flask. The volume above the solution was evacuated, and the reaction was exposed to a large excess of $^{18}O_2$ (250 mL, 11.2 mmol). The solution was cooled to −78 °C for 3 min, and the flask was closed and allowed to stand at room temperature for 1 h. Analysis of the products by gas chromatography/electron impact mass spectrometry showed incorporation of two atoms of ^{18}O into formate **3**. EI-MS: m/z 108 (M^+).

Effect of 2,6-Di-*tert*-butyl-4-methylphenol on Phosphine Oxidation. To each of four NMR tubes was added a solution of tris-(4-fluorophenyl)phosphine (1 μmol) in 400 μL of THF. To two of these tubes was added 2,6-di-*tert*-butyl-4-methylphenol (2.1 μmol) in 400 μL of THF. The contents of the other two tubes were diluted with 400 μL of THF. Just prior to measurement, a solution of catalyst **2** (0.18 μmol, 20 mol %) in 100 μL of THF was added and the contents were vigorously shaken. The reactions were followed by ^{19}F NMR spectroscopy. At 600 s, the reactions containing no phenol were complete, whereas those with phenol had reached only 25 and 27% conversion.

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Phosphine Oxidation in the Presence of 2,4-Di-*tert*-butylphenol. 1. With Catalyst. An NMR tube was charged with tris-(4-fluorophenyl)phosphine (1 μmol) and 2,4-di-*tert*-butylphenol (2.1 μmol) in 800 μL of THF. Just prior to measurement, catalyst **2** (0.18 μmol, 20 mol %) in 100 μL of THF was added and the contents were vigorously shaken. The reaction was followed by ^{19}F NMR spectroscopy. After 2 h, the solvent was evaporated and the solids were taken up in $CDCl_3$. A ^{1}H NMR spectrum confirmed full conversion of the phosphine to phosphine oxide; the phenol remained intact, with no trace of any radical-mediated dimerization.

2. Without Catalyst. A solution of tris(4-fluorophenyl)phosphine (2.5 mg, 0.008 mmol) and 2,4-di-*tert*-butylphenol (1.6 mg, 0.016 mmol) in 4.0 mL of THF was allowed to stand exposed to room light and air. A control experiment was run in parallel which contained no phenol. After 5 days, the reactions were analyzed by ^{1}H NMR spectroscopy, with a few drops of added d_6-benzene. The control experiment had reached 100% conversion to **3** and phosphine oxide, and oxidation of THF to the hydroperoxide was in progress. The reaction containing 2,4-di-*tert*-butylphenol had reached 70% conversion; the phenol remained unchanged.

Phosphine Oxidation in 1,3-Dioxane. A 1.6 mM solution of complex **2** in CH_2Cl_2 was prepared. A 170 μL portion (0.27 μmol, 5 mol %) of this stock solution was added to a vial and the solvent removed with a stream of nitrogen. To each of two clean vials were added tris(4-fluorophenyl)phosphine (1.7 mg, 5.4 μmol) and 2.7 mL of 1,3-dioxane. The contents of one of these vials was added to the metal complex. Phosphine oxidation proceeded at similar rates, reaching completion after about 2 days. Formate **3** was produced in tandem with phosphine oxide, as determined by GC-MS and ^{1}H NMR spectroscopy. ^{1}H NMR (in neat 1,3-dioxane with 50 μL of d_6-benzene): δ 7.80 (s, formate C−H), 4.05 (t, α-CH_2). EI-MS: m/z 104 (M^+).

Decomposition of 2-Hydroperoxytetrahydrofuran. d_6-Benzene (50 μL) was added to a 30 mM solution of 2-hydroperoxytetrahydrofuran[9] (0.7 mL, 0.02 mmol) in THF. Just prior to measurement, catalyst **2** (1.4 mg, 1.0 μmol, 5 mol %) was added, and the reaction was monitored by ^{1}H NMR spectroscopy. Under these conditions, the hydroperoxide decomposed to a mixture consisting mainly of butyrolactone and small amounts of butyrolactol and formate **3**.

The above reaction was repeated in $CDCl_3$ with no THF. The 30 mM solution was concentrated in vacuo, leaving 2-hydroperoxytetrahydrofuran as a clear liquid. The peroxide (20 mg, 0.19 mmol) was dissolved in $CDCl_3$, catalyst **2** (5 mol %) was added, and the reaction was monitored by ^{1}H NMR spectroscopy. Butyrolactone and butyrolactol were observed, along with several unidentified decomposition products.

Decomposition of 2-Methyl-1-phenyl-2-propylhydroperoxide (MPPH) (Chart 3). MPPH[10] (1.0 g, 6.0 mmol) was dissolved in 100 mL of THF, and a solution of catalyst **2** (8 mg, 6 μmol, 0.1 mol %) in 3.7 mL of THF was added. The reaction mixture was stirred until the hydroperoxide was consumed, and the solution was flushed through silica with additional THF to remove the metal complex. After concentration in vacuo, the residue was chromatographed to provide a mixture of benzyl(1-benzyl-1,1-dimethylmethyl)peroxide (**7**) (206 mg, 0.80 mmol) (^{1}H NMR ($CDCl_3$): δ 7.39−7.23 (m, 10H), 4.99 (s, 2H), 2.87 (s, 2H), 1.19 (s, 6H); ^{13}C NMR: δ 138.9, 137.1, 131.7, 130.2, 129.4, 129.3, 128.9, 127.2, 83.4, 77.9, 45.55, 24.7), di(1-benzyl-1,1-dimethylmethyl)peroxide

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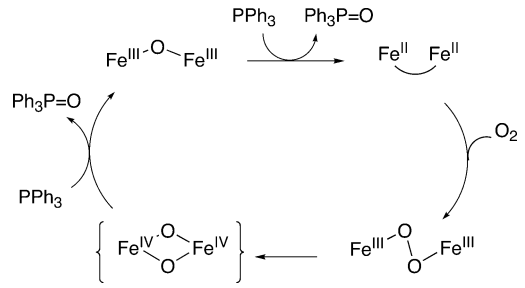
(10) Arends, I. W. C. E.; Ingold, K. U.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1995**, *117*, 4710−4711.

Scheme 1



(**8**) (530 mg, 1.78 mmol) (^{1}H NMR ($CDCl_3$): δ 7.3−7.2 (m, 10H), 2.89 (s, 4H), 1.22 (s, 12H); ^{13}C NMR: δ 138.6, 131.4, 128.9, 127.2, 83.8, 44.9, 24.3; MS(APCI): *m*/*z* 149 ($(M/2)^+$), 133 ($(PhCH\text{-}CMe_2)^+$)), and a small quantity of bibenzyl (**9**) (^{1}H NMR ($CDCl_3$): δ 7.35−7.17 (m, 10H). 2.94 (s, 4H)).

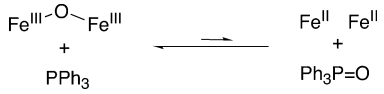
Results and Discussion

Reaction of complex **1** with dioxygen in THF at −78 °C generates an EPR-silent, blue-green species exhibiting Mössbauer and UV parameters consistent with a μ-1,2-peroxo diiron(III) species, analogous to the peroxo intermediate in the oxidation of MMOH.[6] When warmed to room temperature, this species converts to the (μ-oxo)diiron(III) complex **2**. Triphenylphosphine, added before or after generation of 0.1−20 mol % **2** in the presence of dioxygen, is cleanly and quantitatively transformed to its corresponding oxide. Complex **2** is the only spectroscopically observable metal species during the reaction and can itself be isolated and used as a catalyst. From this limited information, we initially considered a cycle similar to that in Scheme 1, which parallels that of MMO (Figure 1).

Among other mono- and dinuclear iron complexes investigated, many of which are close structural analogues of **1** or **2**, only those in which the diiron center is bridged by two terphenyl-derived carboxylate ligands are able to catalyze phosphine oxidation. Notably, whereas doubly terphenylcarboxylate-bridged complexes $[Fe_2(\mu\text{-}O)(\mu\text{-}O_2CAr^{Tol})_2(HBpz_3)_2]$ (**10**) and $[Fe_2(\mu\text{-}O)(\mu\text{-}O_2CAr^{4FPh})_2(HBpz_3)_2]$ (**11**) are catalytically active, the related diacetate compound $[Fe_2(\mu\text{-}O)(OAc)_2(HBpz_3)_2]$ (**13**),[11] and even the mixed acetate-terphenylcarboxylate complex $[Fe_2(\mu\text{-}O)(\mu\text{-}O_2CAr^{Tol})(\mu\text{-}OAc)(HBpz_3)_2]$ (**12**), are inactive. The presence of *two* terphenylcarboxylate ligands is therefore necessary for catalysis. This stringent structural requirement appeared to support a mechanism in which the phosphine substrate is oxidized at the metal center. Electrospray ionization mass spectrometric analysis of analogue **10** indicates facile loss of one carboxylate ligand, suggesting that partial or complete carboxylate dissociation promoted by steric crowding may be a prerequisite to catalysis, perhaps to open space for an incoming substrate. Other terphenylcarboxylate-bridged complexes are believed to undergo similar rearrangements,[12] as does the active site of MMOH.[4]

Nonetheless, we noted several features of the phosphine oxidation that could not be explained by the transformations in Scheme 1. Catalyst **2** is inert to dioxygen in the absence of phosphine, and conversely, **2** does not react with phosphine in the absence of dioxygen; an observable reaction takes place only in the presence of all three components. The cycle in Scheme 1 could accommodate this requirement if complex **2** and triphenylphosphine were to exist in a disfavored equilibrium with the diiron(III) complex **1** and triphenylphosphine oxide (Scheme 2). In such a case, complex **1** would be present in such small quantities as to be experimentally unobservable but perhaps sufficient to facilitate catalytic turnover. This possibility was eliminated by the failure of **1** to react with triphenylphosphine oxide to form **2** and triphenylphosphine.

Scheme 2



The catalysis is also strongly dependent upon solvent. When exposed to air in the presence of 5 mol % catalyst, the phosphine oxidation in THF is complete within a few minutes. In diethyl ether or methyl *tert*-butyl ether, solvents in which the catalyst is significantly less soluble, the reaction proceeds much more slowly, generally reaching about 50% completion after 12 h. No oxidation is observed in toluene, dichloromethane, chloroform, acetone, or acetonitrile. The reactivity in ethers suggested the possibility of a radical mechanism; however, addition of the radical inhibitors 2,6-di-*tert*-butyl-4-methylphenol and 2,4-di-*tert*-butylphenol did not prevent phosphine oxidation, and no products of phenolic hydrogen abstraction were formed, as determined by ^{1}H NMR spectroscopy.

The requirement of ether solvents suggested direct involvement of the solvent in the catalytic cycle. GC-MS and ^{1}H NMR spectroscopic analyses led to the identification of the products 2-hydroperoxytetrahydrofuran (**4**), butyrolactone (**5**), and butyrolactol (**6**). Compounds **4**−**6** form upon treatment of THF with catalyst **2** and dioxygen, even in the absence of a phosphine substrate. The products of this reaction differ from those of uncatalyzed THF autoxidation at 40 °C in air, in which 2-hydroperoxytetrahydrofuran (**4**) forms as essentially the sole product, along with a trace amount of butyrolactone.

We considered the possibility that hydroperoxide **4** is the primary oxidation product and that the phosphine oxide forms in a subsequent reaction with **4**. Indeed, triphenylphosphine and $P(Ar^{4F})_3$ are rapidly and quantitatively converted to the corresponding oxides in the presence of **4**, forming butyrolactol as a byproduct. Further experiments indicated, however, that this reaction is not the source of **6** in the metal-catalyzed reaction. Compounds **4**−**6** do not begin to form until the phosphine oxidation is nearly complete. Careful analysis of the metal-catalyzed reaction revealed a small amount of a fourth THF-derived compound, which was isolated and determined to be the C−C bond-cleavage product 3-hydroxypropylformate (**3**). Real-time monitoring of the reaction by ^{1}H NMR in nondeuterated THF (Figure 2) showed that this ring-opened compound, which incorpo-

(11) Armstrong, W. H.; Spool, A.; Papaefthymiou, G. C.; Frankel, R. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 3653−3667.
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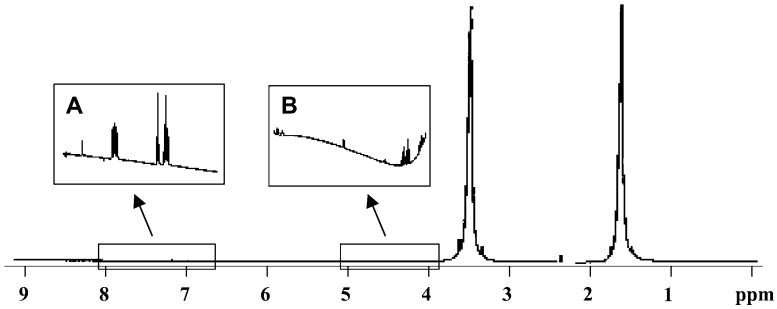


Figure 2. A sample ^{1}H NMR spectrum taken during the phosphine oxidation reaction in neat THF. Only THF is visible in the full spectrum. Expansion of the baseline area in the region δ 6.5−8.5 shows O═P(Ar^{4F})$_3$ and the formate CH of THF oxidation product 3-hydroxypropylformate (**3**), as well as d_6-benzene (inset A); 2-hydroperoxytetrahydrofuran (**4**), butyrolactone (**5**), butyrolactol (**6**), and compound **3** show peaks between δ 4.0 and 5.5 (inset B).

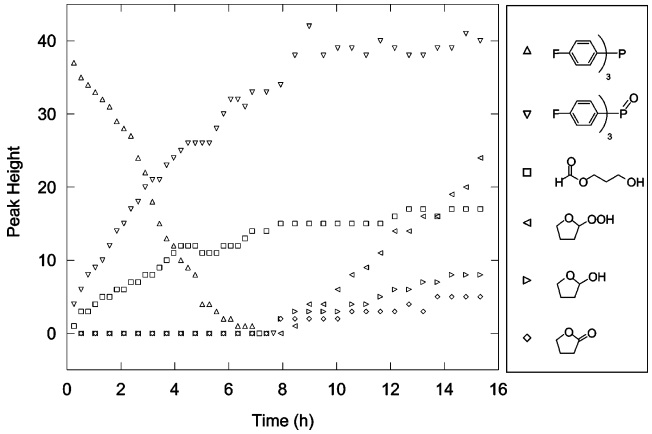


Figure 3. Consumption of phosphine and formation of phosphine oxide and THF oxidation products during the course of the oxidation reaction in the presence of **2**. Conditions: 2.0 mM tris(4-fluorophenyl)phosphine, 0.10 mM **2**, and THF as solvent. The reaction was run in the NMR tube with 50 μL of d_6-benzene added as a magnetic lock.

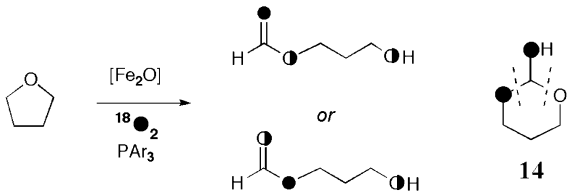
rates two new oxygen atoms, is the sole THF oxidation product formed during phosphine oxidation. Compound **3** is produced cleanly and catalytically in a 1:2 stoichiometry with respect to the phosphine oxide (eq 1). It ceases to form

$$2Ar_3P + 2O_2 + THF \xrightarrow[\text{cat.}]{[Fe_2O]} 2Ar_3P{=}O + HC(O)OCH_2CH_2CH_2OH \quad (1)$$

only when the phosphine supply is exhausted, at which point compounds **4**−**6** begin to accumulate. The kinetic data, summarized in Figure 3, implicate the phosphine as a sacrificial reductant in the C−C bond-cleavage reaction. To the best of our knowledge, although carbon−carbon bond cleavage between the 2 and 3 positions of THF has been reported,[13,14] conversion to compound **3** is unprecedented. In fact, efficient methodology for the selective synthesis of monoformylated diols is conspicuously lacking in the literature.

Experiments conducted in the presence of $^{18}O_2$ using P(Ar^{4F})$_3$ as substrate resulted in 100% incorporation of ^{18}O at one of the formate oxygen positions of **3** and 50% incorporation at the other two oxygen positions (Scheme 3).

Scheme 3



The mass spectra of **3** generated from oxidations in $^{16}O_2$ vs $^{18}O_2$ are compared in Figure 4. The M^+ peak from the $^{18}O_2$ experiment occurs at m/z = 108, four mass units above the molecular weight of [^{16}O]-hydroxypropylformate, indicating that two ^{18}O atoms have been incorporated. Its low intensity is typical of primary alcohols. The fragmentation patterns are characteristic of formates and primary alcohols. The fragment [HC(O)OCH$_2$CH$_2$] results from loss of hydroxymethylene; protonation of this fragment gives an ion of m/z = 74, observed in the mass spectrum of the ^{16}O-formate standard. In the ^{18}O labeling experiment, peaks of equal intensity are seen for m/z = 76 and 78, indicating incorporation of 1.5 ^{18}O atoms into this fragment. Elimination of formic acid gives fragments [CH$_2$CHCH$_2$O] and [CH$_2$CHCH$_2$OH], which ionize to give m/z = 57 and 58. In the labeling experiment, these peaks remain, but signals at m/z = 59 and 60 of equal intensity are also present, indicating 50% incorporation of ^{18}O at the terminal hydroxyl group. The equal distribution of the label between the hydroxy and formate sites suggests a symmetric intermediate of general structure **14**, which is further discussed below. The signal at m/z = 88 is the molecular ion peak of [^{18}O]-butyrolactone, which overlaps slightly with that of formate in the gas chromatogram. ^{18}O was incorporated into 100% of the phosphine oxide.

Formate **3** is also generated, together with the phosphine oxide, in the autoxidation of PAr$_3$ (Ar = Ph, Ar^{4F}) in the absence of catalyst **2**. Provided that glassware is thoroughly rinsed with freshly distilled THF just before use and the reaction vial is exposed to ordinary room light, the autoxidation of P(Ar^{4F})$_3$ reaches completion within 2−3 days (as compared with 5−10 min with 5 mol % catalyst). If the glassware is not rinsed with freshly purified solvent, the oxidation is often complete in under 12 h, presumably due to initiators present on the glass in trace quantities. The reaction requires light; in an experiment where the solution was kept in the dark, only unoxidized phosphine was detected after 23 days. As in the process catalyzed by **2**, formation

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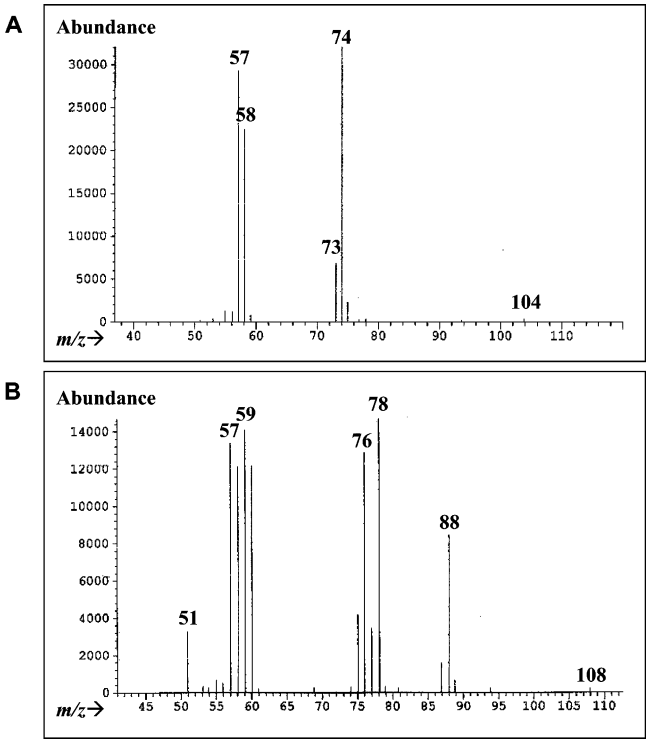


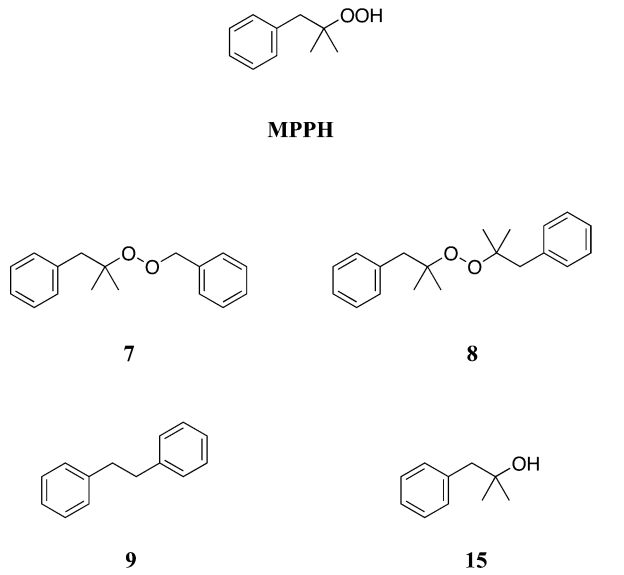
Figure 4. (A) EI-MS of formate **3**. (B) EI-MS of compound **3**, derived from THF and $^{18}O_2$.

of **3** ceases after phosphine oxidation is complete, and 2-hydroperoxytetrahydrofuran begins to build up. In the absence of **2**, however, the hydroperoxide is the only product formed after phosphine consumption. Thus, apart from the rate acceleration in the presence of **2**, the only difference between the metal-catalyzed and uncatalyzed processes is the metal-catalyzed formation of butyrolactol and butyrolactone following phosphine consumption. These compounds arise from decomposition of hydroperoxide **4** by complex **2**, as demonstrated by treatment of independently synthesized **4** with **2** in either THF or $CDCl_3$.

To address whether the decomposition of **4** involves a radical or nonradical pathway, we investigated the reaction of **2** with the hydroperoxide probe MPPH.[10] Reaction of MPPH with 0.1 mol % **2** in THF results only in products of homolytic O−O bond cleavage, predominantly compounds **7** and **8**, along with a small amount of bibenzyl (**9**). No products containing the tetrahydrofuranyl moiety are formed. Alcohol **15** (Chart 3), the expected product of heterolytic decomposition, is not observed. Therefore, it is likely that decomposition of **4** also occurs by a homolytic O−O bond-cleavage process.

The observation of nearly identical reaction pathways in the presence or absence of catalyst under two different reaction conditions—i.e., in the presence and the absence of phosphine—strongly suggests that a common intermediate is at work in all four cases. The most plausible role for catalyst **2** is to serve as an initiator in a non-metal-centered process, probably involving free radicals. The mechanism in Scheme 4 proposes a common peroxy radical intermediate (**16**) for both phosphine oxidation and phosphine-free pathways. In this mechanism, complex **2** initiates the process

Chart 3



by abstracting a hydrogen atom from the α position of THF and possibly by promoting its reaction with dioxygen to provide peroxy radical **16**.

That **4** is not observed as a product until the phosphine substrate has been fully converted requires much faster consumption of **16** by the phosphine than by THF solvent. This difference in rates is expected. The reactivities of secondary ether peroxy radicals, such as **16**, are similar to those of structurally related secondary hydrocarbon peroxy radicals,[15] which are 4−8 times more reactive than *tert*-butylperoxy radicals in addition reactions.[16] If we assume a similar difference in reactivity of these peroxy radicals toward PPh_3 and $P(Ar^{4F})_3$, for which the rates of reaction with *t*-BuOO$^\bullet$ have been measured,[17] the rate constants for [**16** + PAr_3 → products] should be 10^4-10^5 M^{-1} s^{-1} at 298 K. The reaction of **16** with these triarylphosphines should therefore easily outcompete the rate-limiting propagation step in the autoxidation of THF, in which peroxy radical **16** abstracts a hydrogen atom from the ether solvent (k_p = 1.1 M^{-1} s^{-1}).[18] Thus, rapid reaction of triphenylphosphine with **16** will provide a transient but comparatively more stable phosphoranyl radical **17**. Loss of phosphine oxide drives the fragmentation of this species with concomitant C−C bond cleavage to give radical **18**, which is stabilized by the presence of two oxygen atoms adjacent to the radical center.

Radical **18** is an intermediate in oxidations of 1,3-dioxane, a known source of formate **3**.[19−24] Reaction of **18** with O_2

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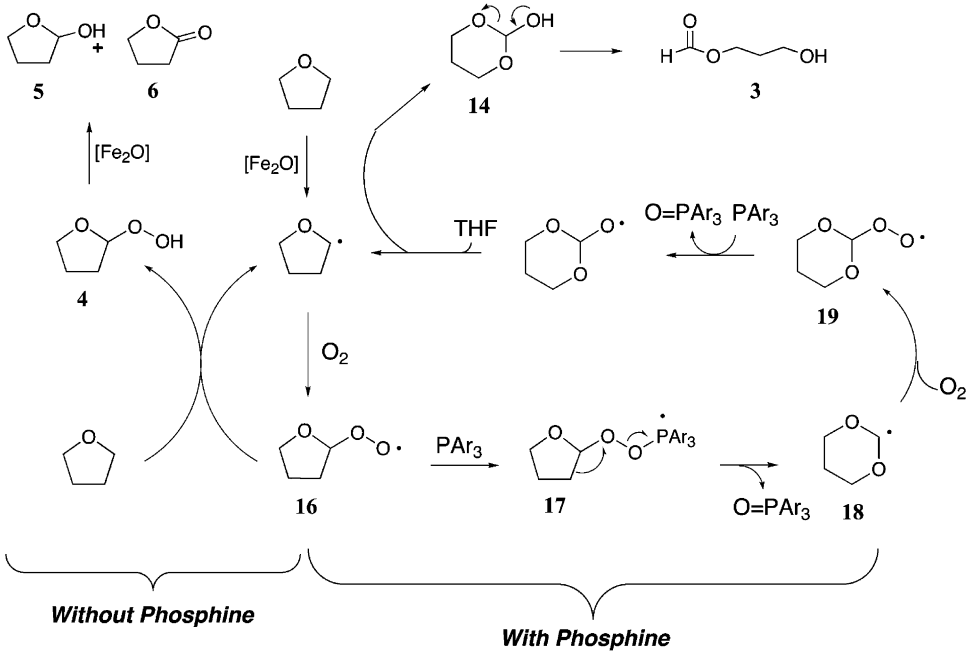
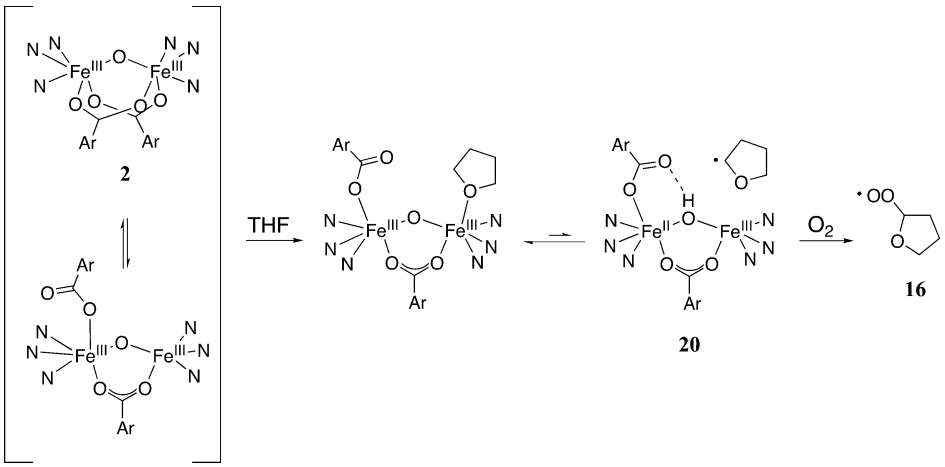
Scheme 4



Scheme 5



provides radical **19**, which is reduced by a second equivalent of phosphine and abstracts a hydrogen atom from THF, propagating the cycle (Scheme 4). The resulting symmetric compound, **14**, is unstable and will cleave at either of the two orthoformate C−O bonds to give formate **3**, accounting for the result of the ^{18}O labeling study. Control reactions confirmed that phosphine oxidation in 1,3-dioxane does indeed generate formate **3**. The reaction proceeds at similar rates in the presence or absence of catalyst **2**. This solvent would therefore appear to be a poor substrate for **2**, and the observed reaction is probably a standard free-radical autoxidation process, consistent with Scheme 4. After the consumption of phosphine, or in its absence, peroxy radical **16** abstracts a hydrogen atom from THF to give hydroperoxide **4**, which is then slowly decomposed by catalyst **2**.

The preference of catalyst **2** for THF over other ethers strongly suggests a direct and specific interaction between the solvent and the dimetallic center. The steric bulk of the two bridging carboxylates should facilitate the ligand dissociation required for THF coordination; the lability of terphenylcarboxylate ligands has been observed in NMR studies of related carboxylate-bridged diiron complexes[12] as well as in the ESI-MS spectrum of catalytically active analogue **10** (vide supra). A plausible initiation mechanism would parallel the M^{3+}/M^{2+} redox mechanism operative in one-electron oxidations of electron-rich organic substrates by Fe^{3+} and Co^{3+} salts[25−28] and in Fe^{3+}- and Mn^{3+}-promoted autoxidations of organic solvents.[29] We propose the sequence illustrated in Scheme 5, whereby hydrogen atom abstraction from the coordinated solvent molecule results in a hydroxo-bridged, mixed-valent Fe(II)Fe(III) species, **20**, and a THF

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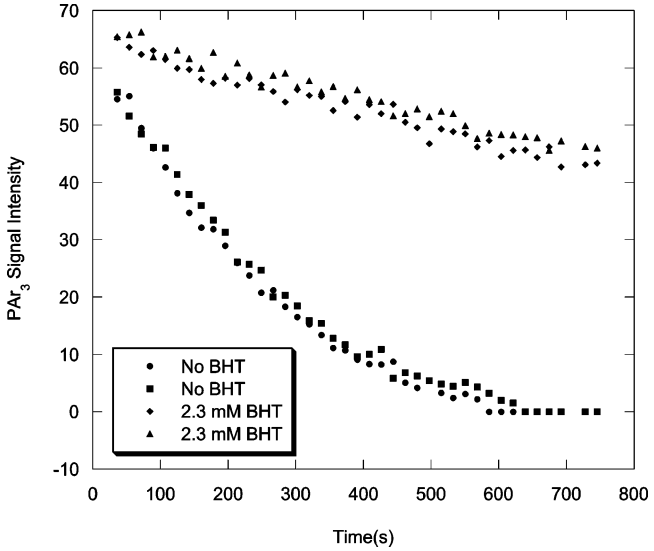


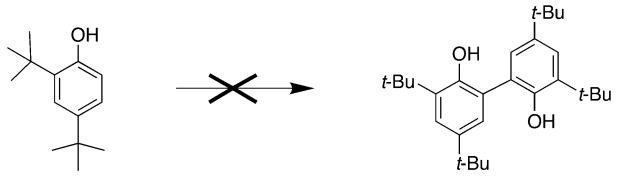
Figure 5. Effects of 2,6-di-*tert*-butyl-4-methylphenol (BHT) on the rate of tris(4-fluorophenyl)phosphine oxidation. Conditions: 0.83 mM $P(Ar^{4F})_3$, 0.17 mM **2**, and THF as solvent; the reaction was run in air.

radical. The latter can react with dioxygen to give peroxy radical **16** either within or outside the metal coordination sphere; the former might react with dioxygen or peroxides to regenerate the (μ-oxo)diiron(III) species.[30]

Last, we revisited the experiments with radical inhibitors 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 2,4-di-*tert*-butylphenol. It was previously reported[6] that addition of BHT to the triphenylphosphine oxidation reaction in the presence of 20 mol % catalyst does not inhibit the reaction. We reinvestigated the effect of BHT and found that, although phosphine oxidation indeed occurs in its presence, the reaction rate is significantly retarded (Figure 5).

We had also previously observed that 2,4-di-*tert*-butylphenol had no effect on the catalyzed phosphine oxidation. Reexamination of the effects of this radical inhibitor revealed that, even in an uncatalyzed autoxidation of $P(Ar^{4F})_3$, 2,4-di-*tert*-butylphenol does not react to form the expected radical product **21** (Scheme 6) and remains unchanged throughout the phosphine oxidation process. This result implies that, if radicals are involved in the reaction, 2,4-di-*tert*-butylphenol is unsuitable for their detection under the conditions employed. The reasons for its failure may be debated, but it is possible that the phenoxyl radical does not reach sufficiently high concentrations to dimerize at a competitive rate. The above experiments demonstrate, however, that our earlier experiments with radical probes do not constitute evidence for a metal-centered oxidation in this system.

Scheme 6



21

Conclusions

The present study reveals that the catalytic conversion of triarylphosphines and dioxygen to triarylphosphine oxides in the presence of diiron complexes **1** or **2** is coupled to oxidation of THF to afford the unprecedented ring-opened product 3-hydroxypropylformate (**3**). The corresponding uncatalyzed reaction, while slow, is similarly coupled and provides the same products. Labeling studies with $^{18}O_2$ and experiments in 1,3-dioxane support passage through the cyclic intermediate **14**, which results from carbon−carbon bond cleavage between the 2 and 3 positions of THF. These and additional findings provide evidence for a solvent-assisted autoxidation reaction initiated by hydrogen abstraction from THF by catalyst **2**. We cannot completely exclude the possibility that parallels between catalyzed and uncatalyzed systems are coincidental and that the diiron complex does in fact directly mediate the phosphine oxidation. Indeed, a carboxylate-bridged diiron complex related to **2** has now been developed in our laboratory which is capable of catalytic phosphine oxidation in acetonitrile, dichloromethane, and benzene; the last solvent, especially, is less likely to propagate radical chemistry.[31] The difficulty in distinguishing between radical and metal-centered pathways in catalytic oxidation chemistry is highlighted by recent reinvestigations of several iron-based systems originally believed to operate by nonradical mechanisms.[10,32,33] The present report joins the aforementioned works as a reminder that understanding and controlling O−O bond reactivity will continue to challenge chemists at the most fundamental level into the future.

Acknowledgment. This work was supported by grants from the National Science Foundation and the National Institute of General Medical Sciences. R.F.M. is an NIH postdoctoral fellow on National Cancer Institute Training Grant T32CA009112 and E.Y.T. held a Fulbright fellowship.

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