Photooxidation of Mixed Aryl and Biarylphosphines

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Abstract

6, 7, 8, 9: $R^1 = R^2 = $ *tert*-butyl   **6**: *Intra*molecular oxidation preferred
10, 11, 12, 13: $R^1 = R^2 = $ cyclohexyl   **10**: *Inter*molecular oxidation preferred
                                    8, 12: Only insertion into alkyl P-C bond observed

Aryl phosphines and dialkylbiaryl phosphines react with singlet oxygen to form phosphinate esters. For mixed arylphosphines, the most electron-rich aryl group migrates to form the phosphinate, while for dialkylbiaryl phosphines migration of the alkyl group occurs. Dialkylbiaryl phosphines also yield arene epoxides, especially in electron rich systems. Phosphinate ester formation is increased at high temperature while protic solvents increase the yield of epoxide. The product distribution provides evidence for Buchwald's recent conformational model for the aerobic oxidation of dialkylbiaryl phosphines.

Phosphadioxiranes are highly reactive heteroatom-containing peroxides, and belong to what Greer et al. have aptly called "rather exotic types of cyclic peroxides".[1] It is now well-established that they are the primary intermediates in the reaction of singlet dioxygen with phosphines.[2,3] In addition, at very high temperatures, phosphadioxiranes are probably formed during the reaction of triplet dioxygen with phosphines.[4] Intermolecular oxygen atom transfer from these highly unstable intermediates to the starting phosphine leads to phosphine oxide formation. In addition to this process, phosphadioxiranes may undergo a variety of interesting reactions, including oxygen atom insertion into the aryl P-C bond to form phosphinate esters, and, in a few cases, arene epoxidation.[5,2b,2c] Several theoretical studies suggest that phosphadioxiranes should be electrophilic oxidants.[3] However, the scope of oxygen atom transfer reactions from phosphadioxirane as well as the regioselectivity, and effects of temperature and solvent are not known. For example, the photooxidation of arylphosphines with different aryl groups attached to the phosphorus atom

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has not been studied, i.e. it is not known if the formation of phosphinate esters is regioselective. Furthermore, there have been no reports of photooxidation of several other important classes of phosphines such as phosphines bearing biaryl ligands. Intramolecular oxygen atom insertion into the P-C bond and arene epoxidation might ultimately be useful reactions for the functionalization of such phosphines, if the scope and regioselectivity of these reactions were known, and if the competing intermolecular oxygen atom transfer to form phosphine oxide could be limited. In this paper, we present a detailed investigation of product distribution, regioselectivity, solvent and temperature effects of the reactions of phosphadioxiranes generated from singlet oxygen and a variety of different phosphines. We show that oxygen atom insertion in mixed (i.e. bearing different aryl and/or alkyl groups) phosphines is in fact regioselective. We also investigate how solvent and temperature effects can be used to maximize the yield of either phosphinate ester or arene epoxide.

Photooxidation of aryl phosphines bearing large substituents in the ortho position of the aryl ligand predominately yield phosphinate esters from intramolecular oxygen atom insertion into the P-C bond.[2b] Arylphosphines without bulky substituents give mainly phosphine oxide upon reaction with singlet oxygen. The intermediate phosphadioxirane is presumed to be an electrophilic oxidant, but there is little experimental evidence, as phosphines bearing different aryl ligands have not been studied. We have therefore begun our study of the photooxidation of mixed phosphines by investigating the reaction of bis(ortho-methoxyphenyl)-phenylphosphine (**1**) with singlet oxygen. Photooxidation of **1** at room temperature (solvent = toluene-d_8, sensitizer = tetraphenylporphyrin (TPP), phosphine concentration = 1 mM to 20 mM, Tungsten-Halogen lamp, cut-off filter at 493 nm) leads to only two products, namely (ortho-methoxyphenyl) phenyl ortho-methoxyphenyl-phosphinate (**2**), and bis(ortho-methoxyphenyl)-phenylphosphine oxide (**3**).

Both products were characterized by ^{1}H and ^{31}P NMR, and their identities were confirmed by X-ray molecular structures (see supporting information). The insertion reaction leading to formation of **2** is completely regioselective. We did not observe any oxygen atom insertion into the P-C bond bearing the unsubstituted phenyl ring. Furthermore, unlike for binaphthyl phosphines,[2c] we did not observe any hydroxylation of the aromatic ring.

Dialkylbiaryl phosphines have been widely used in Pd-catalyzed cross-coupling reactions, in part because they are rather resistant towards oxidation.[6,7] Buchwald et al. have recently suggested that the biaryl ligand as well as substituents on the 2' and 6' position of the biaryl ring play a key role in the susceptibility – or lack thereof – towards reaction with triplet oxygen.[6] The reactivity of these phosphines with singlet oxygen has not been studied to date. *A priori*, a wide range of possible products can be envisioned, i.e. oxygen atom insertion into the P-C bond of either the alkyl or biaryl ligand, formation of arene epoxides, and simple formation of phosphine oxide by intermolecular oxygen atom transfer. Of particular interest is the question of whether alkyl or aryl group migration is preferred in these compounds; alkyl migration in a phosphadioxirane has not previously been reported.

The reaction of unsubstituted 2-di-t-butyl biphenylphosphine (**4**) with singlet dioxygen in deuterated toluene at room temperature yields the corresponding phosphine oxide (**5**) as the sole product (see Table 1). No epoxidation or insertion products (i.e. via alkyl or aryl migration) were observed. Even at high temperature where aryl migration may be more favorable (see below) the reaction of singlet oxygen with biphenylphosphine **4** in toluene yields phosphine oxide **5** as the only product.

In marked contrast to the unsubstituted 2-di-t-butyl biphenylphosphine **4**, the bulky highly substituted di-t-butyl tri-isopropyl biphenylphosphine **6** reacts with singlet dioxygen to form phosphine oxide **7** and phosphinate **8** (see Scheme 2), as well as a very small amount of

arene epoxide **9** in toluene-d_8. The latter compound is readily identified by the ^{1}H NMR signals of the vinyl protons of the oxidized ring which give rise to singlets at 5.70 and 4.70 ppm. Even at room temperature, at 24 mM starting concentration of **6**, the phosphinate product **8** predominates (Table 1). The phosphinate ester **8** is of special interest: We were able to establish that migration in phosphines containing both alkyl and aryl ligands, migration of the alkyl group is favored over the aryl group. The ^{1}H NMR spectrum of a purified sample of **8** shows that the hydrogens of the *tert*-butyl group directly attached to the phosphorous are split by the phosphorous atom into a doublet (J = 15.9 Hz) at 0.97 ppm. The hydrogen atoms of the *tert*-butyl group bound to the oxygen, on the other hand, exhibit no coupling to the phosphorous atom and thus occur as a singlet at 1.42 ppm. In contrast to phosphinate **8**, the hydrogens of both *tert*-butyl groups of phosphine oxide **7** are chemically equivalent and appear as a doublet (J = 13.3 Hz) at 1.25 ppm. Additional details of the spectroscopic analyses are given in the supporting information.

Interestingly, the reactivity of the related dicyclohexyl tri-isopropyl biphenylphosphine **10** is rather different. During photooxidation of **10** at room temperature, formation of phosphine oxide **11** predominates relative to phosphinate ester **12**, i.e. intermolecular oxygen atom transfer is much more facile than for the di-t-butyl phosphine **6**. Furthermore, we observed a considerable amount of epoxide **13** (22% at room temperature for initial concentration of **10** of 24 mM, Table 1). The epoxide could be formed either by intramolecular or intermolecular oxygen atom transfer from the intermediate phosphadioxirane. If the epoxidation proceeds by an intramolecular pathway, the product ratio of epoxide and phosphine oxide vs. starting phosphine concentration (at low conversion of phosphine) can be expressed by equation (1), where k_{epox} is the rate constant for epoxide formation from phosphadioxirane, and k_o is the rate constant for intermolecular oxygen atom transfer to give two equivalents of phosphine oxide:

$$\frac{[\mathbf{11}]}{[\mathbf{13}]} = \frac{2k_o[\mathbf{10}]}{k_{epox}}$$

(1)

A plot of the product ratio **11**/**13** vs. **10** gave a straight line with a slope ($2k_o/k_{epox}$) of 110 M^{-1}, confirming that epoxidation is indeed an intramolecular process. The relative rate ratio of intramolecular epoxidation vs. intermolecular oxygen atom transfer is 55 M^{-1}, and intermolecular oxygen atom transfer predominates, except at very low concentrations of **10** (2 mM or less).

Even though the photooxidation product distribution for phosphines **6** and **10** is very different, we determined that their rate constants for singlet oxygen removal k_T are very similar (Table 1, second column). This implies that the approach of the singlet oxygen molecule to phosphines **6** and **10** is not affected by the difference of the alkyl ligands. Hence the origin of the different product distribution results from steric factors of the intermediate phosphadioxirane complexes and their interaction with starting phosphines. Buchwald and Barder recently noted that phosphine **6** is considerably more resistant to reaction with ground state (triplet) oxygen than phosphine **10**.[6] They investigated the barrier for rotation around the P-C bond of the biaryl ligand such that the phosphorus lone pair (or peroxidic intermediate) points away from the large biphenyl ligand. For compound **6**, this rotational barrier is much larger than for compound **10** (12.6 kcal/mol vs. 6.3 kcal/mol).[6] Furthermore, they determined that the "away conformer" (where the phosphorus lone pair or the dioxygen moiety of a peroxidic intermediate points away from the bulky biaryl ring system) is much more disfavored for compound **6** relative to compound **10**. Our observations for the product distribution during the photooxidation of **6** and **10** provide strong evidence for Buchwald's model. Since compound **6** has a much more restricted rotation and the "away conformer" is

more strongly disfavored, intermolecular oxygen atom transfer to unreacted starting material is much more difficult, and intramolecular oxygen atom insertion predominates.

Replacement of the isopropyl groups of the biaryl phosphines with isopropoxy groups also has a drastic effect on the reactivity of the intermediate phosphadioxirane: reaction of diisopropoxy biphenylphosphine **14** with singlet oxygen in toluene-d_8 gives epoxide **15** in nearly quantitative yield (Scheme 3).

Epoxide **15** is stable at 0 °C for weeks, but decomposes into a complex mixture at room temperature. The rate of singlet oxygen removal (k_T) by this phosphine is faster compared to the other biaryl phosphines, due to the electron-donating character of the isopropoxy groups.

The product distribution in all of the photooxidation reactions reported here is highly sensitive to temperature and solvent effects. In general, at higher temperature, the yield of phosphinate ester is increased, and that of phosphine oxide is diminished. Details are given in Table 1. Thus, if the phosphinate esters are desired products, carrying out the photooxidation at high temperature and low starting material concentrations will result in the highest yields of phosphinate esters.

The presence of protic solvents leads to protonation of the intermediate phosphadioxirane, and formation of hydroperoxy phosphoranes.[2a,2b,3b] Very little is known about the chemistry of the latter species. To investigate the reactivity of the hydroperoxy phosphorane, we added up to 20% (by volume) of CD_3OD to phosphines **6** and **10** prior to carrying out the photooxidation. Under these conditions, phosphinate ester formation is suppressed while the yield of epoxide and phosphine oxide is increased (Table 3). Clearly, the hydroperoxy phosphorane is much more capable than phosphadioxirane to form arene epoxides. Hence, if the latter product is desired, one can simply carry out the photooxidation under protic conditions. In general, despite the fact that photooxidation of biaryl phosphines may lead to multiple products, judicious choice of temperature and solvent system can maximize the yield of one of the oxidation products over the others.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

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Acknowledgments

Scheme 1.
Reaction of Bis(ortho-methoxyphenyl)-phenylphosphine (**1**) with Singlet Oxygen

Scheme 2.
Photooxidation of Dialkyl Triisopropyl Biphenylphosphines

Scheme 3.
Photooxidation of Diisopropoxy Biphenylphosphine

Table 1

Product Distribution and rates of Singlet Oxygen Removal (k_T) for Photooxidation of Dialkylbiaryl Phosphines

starting phosphine	$k_T \times 10^{-7}$ $(M^{-1}sec^{-1})^a$	phosphine oxide $(\%)^b$	phosphinate $(\%)^b$	arene epoxide $(\%)^b$
4	1.2 ± 0.1	100 ± 1	0	0
6	0.81 ± 0.05	13 ± 0.3	84 ± 0.1	2 ± 0.3
10	0.63 ± 0.05	65 ± 4	13 ± 5	22 ± 4
14	2.1 ± 0.1	0	0	100 ± 1

[a] k_T values are averages of three runs, error is one standard deviation.

[b] All reactions were performed in an NMR tube using 1 mL solutions of biphenylphosphine (24 mM) in toluene-d_8, concentration of TPP sensitizer = 0.13 mM. Relative amount of products were calculated (average of three runs, error is one standard deviation) using ^{31}P NMR integrations.

Table 2

Product Distribution During Photooxidation of Dialkylbiaryl Phosphines at Different Temperatures

starting phosphine	T (°C)	phosphine oxide (%)	phosphinate (%)	arene epoxide (%)
6	22	13 ± 0.3	84 ± 0.1	2 ± 0.3
6	60	8 ± 1	90 ± 1	2 ± 0.3
10	22	65 ± 4	13 ± 5	22 ± 4
10	60	36 ± 2	44 ± 1	20 ± 2

All reactions were performed in an NMR tube using 1 mL solutions of biphenylphosphine (24 mM) in toluene-d8. Relative amount of products were calculated (average of three runs, error is one standard deviation) using ^{31}P NMR integrations.

Table 3

Product Distribution During Photooxidation of Dialkylbiaryl Phosphines Upon Addition of CD$_3$OD

starting phosphine	CD$_3$OD in toluene-d_8	phosphine oxide (%)	phosphinate (%)	epoxide (%)
6	0	13 ± 0.3	84 ± 0.1	2 ± 0.3
6	2%	27 ± 3	66 ± 5	8 ± 2
6	20%	62 ± 5	6 ± 0.6	32 ± 5
10	0	65 ± 4	13 ± 5	22 ± 4
10	2%	53 ± 3	8 ± 0.4	39 ± 4
10	20%	11 ± 1	0	89 ± 1

All reactions were performed in an NMR tube using 1 mL solutions of biphenylphosphine (24 mM). Relative amount of products were calculated (average of three runs, error is one standard deviation) using ^{31}P NMR integrations.