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Synthesis of aromatic phosphates via cycloaddition of phosphate dienes

MeeKyoung Kim and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, USA

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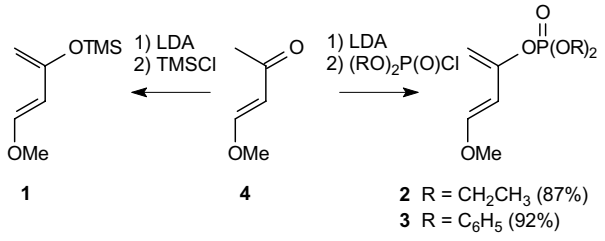
Abstract—Cycloadditions of phosphate dienes and quinones can be used to generate aromatic phosphates. Diethyl 3-methoxy-1-methylene-2-propenyl phosphate shows reactivity, stability, and regioselectivity comparable to the corresponding silyloxy diene. Because the phosphate ester in the product originates in the diene, cycloadditions with quinones will place this ester regiospecifically in the B-ring and allow facile distinction between the B- and A-ring oxygens of the cycloadduct.

The Diels–Alder reaction is one of the more powerful reactions in organic synthesis,[1] and can be used to prepare cyclic, heterocyclic, and aromatic targets. Its appeal derives not only from the fact that two carbon–carbon bonds can be formed in a single operation, but also from the high regio- and stereoselectivity that can be obtained in the process. The selectivity of the cycloaddition is highly dependent upon the diene substituents, and one of the patterns leading to an electronically favorable process is found in the silyloxy diene often referred to as Danishefsky's diene (**1**, Scheme 1).[2] In contrast to the number of reports on applications of silyloxy dienes, such as compound **1**, the corresponding phosphate dienes (e.g., **2** and **3**) have been little studied,[3,4] even though they can also be prepared from the commercial methyl ketone **4**.[4] Because a phosphate diene might be used to introduce a phosphate directly into a cycloadduct in a regiospecific manner, these dienes were of special interest to us. Numerous synthetic transformations have been reported for vinyl phosphates, including conversion to other functional groups,[5] carbon–carbon bond forming reactions,[6] or rearrangement to β-keto phosphonates (vide infra). To enable parallel studies on the reactivity of aromatic phosphates, and to illuminate the potential of phosphate dienes as synthons for aromatic phosphates, their reactivity with some representative dienophiles has been examined.



Scheme 1. Synthesis of phosphate dienes.

One family of aromatic phosphates might be attainable through reaction of a phosphate diene with quinone dieneophiles (Scheme 2), and this strategy allows facile distinction between the A- and B-ring oxygens of the cycloadduct. A number of products might be expected from such reactions depending upon the work-up employed and the quinone substituent if one is present. With benzoquinone itself, regiochemistry is not an issue in the cycloaddition, but unsymmetrical quinones could lead to more complex product mixtures. As shown in Scheme 2, with a substituted benzoquinone two initial cycloadducts are possible (**6** and **7**). These products are not aromatic, but tautomerization and loss of methanol would afford the regioisomeric hydroquinones **8** and **9**, and subsequent oxidation would afford the quinones **10** and **11**. Formation of the final quinone would depend on the duration of exposure to air during isolation and purification.[7]

The phosphate dienes **2** and **3** were readily prepared by treatment of the methyl ketone **4** with LDA at −78 °C, followed by reaction with diethyl or diphenyl

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* Corresponding author. Tel.: +1 319 335 1365; fax: +1 319 335 1270; e-mail: david-wiemer@uiowa.edu

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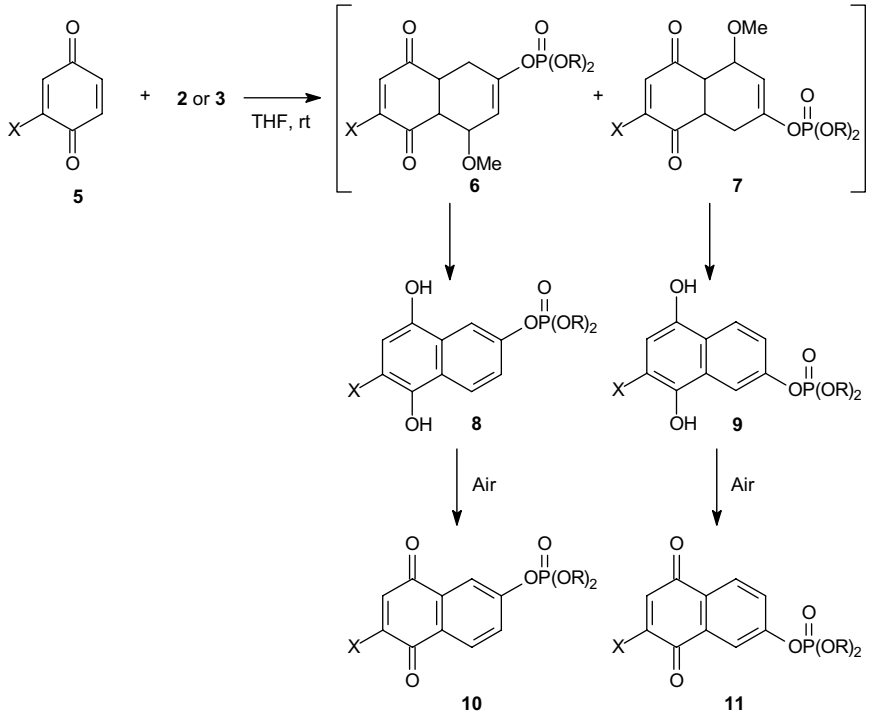


Scheme 2. Potential reactions of phosphate dienes.

phosphorochloridate (Scheme 1). To begin this study, the phosphate diene **2** was allowed to react with several potential dienophiles (**12**–**15**). Diene **2** undergoes facile reaction when treated with benzoquinone (**12**), or with methyl- or chlorobenzoquinone (**13** or **14**), at room temperature (Table 1). Acetylene **15** also reacts smoothly.

The reaction of diene **2** with benzoquinone afforded both the hydroquinone **16**[8] and the quinone **17**[9] after cycloaddition and elimination of methanol in situ, purification of the reaction mixture by column chromatography, and (presumably) air oxidation, in 57% and 26% yields, respectively. When column chromatography was continued over a longer period of time, compound **17** was the only observed product. It was difficult to establish the extent of oxidation involved during the reaction itself by TLC analysis, because compound **16** was readily converted to compound **17** upon exposure to air.

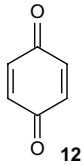
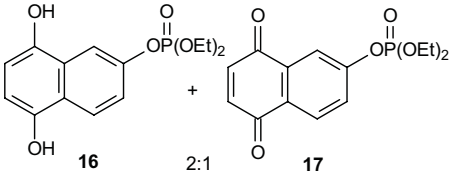
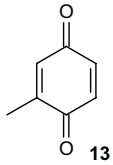
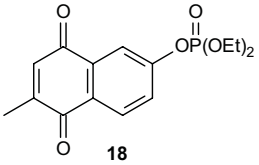
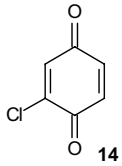
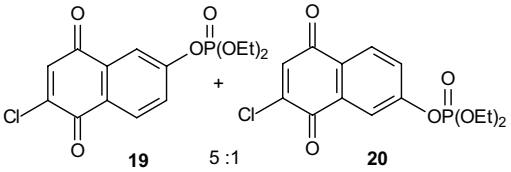
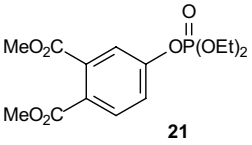
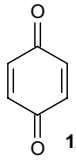
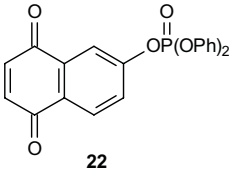
The reactions of diene **2** with methyl- or chlorobenzoquinone proved to be regioselective. Treatment of diene **2** with methylbenzoquinone in THF at room temperature gave compound **18** in 62% yield as a single product after column chromatography. When this reaction was conducted at 45–50 °C, traces of the regioisomeric cycloadduct could be observed in the ^{1}H NMR spectrum of the initial product but it was not possible to isolate the minor isomer. Both regioisomers **19** and **20** were obtained from cycloaddition of diene **2** with chlorobenzoquinone (**14**) in THF at room temperature, in 64% total yield and a 5:1 ratio based on analysis of the ^{1}H NMR spectrum. At a lower reaction temperature (−13 to 10 °C), this reaction afforded both regioisomers in a 10:1 ratio but only in 26% yield after column chromatography.

The structure assignment of compound **18** was based on data from a variety of NMR experiments. The important diagnostic signals and correlations are shown in Figure 1A. The key correlations in the HMBC experiment were observed between a carbon resonance at 184.4 ppm and hydrogen resonances at δ 8.11, 6.08, and 2.20, and between a carbon resonance at 183.9 ppm and a hydrogen resonance at δ 7.82. Similarly, the major product **19** was assigned as the structure shown in Figure 1B. In this case, the key correlations in the HMBC experiment were observed between a carbon resonance at 181.7 ppm and a hydrogen signal at δ 7.86, and between a carbon resonance at 176.8 ppm and hydrogen signals at δ 8.19 and 7.23.

It also should be possible to obtain an aryl phosphate through reaction of a phosphate diene with an acetylenic dienophile. For example, the reaction of dimethyl acetylenedicarboxylate with diene **2** yielded compound **21** in 73% yield after cycloaddition and elimination of MeOH. While this product could be obtained through reaction of this acetylene with the silyloxy diene **1**, such a sequence is inherently a longer route to the aryl phosphate, since after cycloaddition it would require hydrolysis of the silyl group and phosphorylation.

The diphenyl phosphate diene **3** was also examined briefly,[4] but appeared to offer little benefit in these reactions vis-à-vis the diethyl ester **2**. For example, cycloaddition of phosphate diene **3** with benzoquinone gave compound **22** in 54% yield after column chromatography. While the phenyl esters may increase the reactivity of this diene, the benefit is minimal because it appeared to have limited stability. Diene **3** decomposed within a few days even upon storage below 0 °C.

Table 1. Reaction of phosphate dienes with benzoquinones

Dienophile	Diene	Product(s)	Yield (%)
 **12**	**2**	 **16** 2:1 **17**	83
 **13**	**2**	 **18**	62
 **14**	**2**	 **19** 5 :1 **20**	64
 **15**	**2**	 **21**	73
 **12**	**3**	 **22**	54

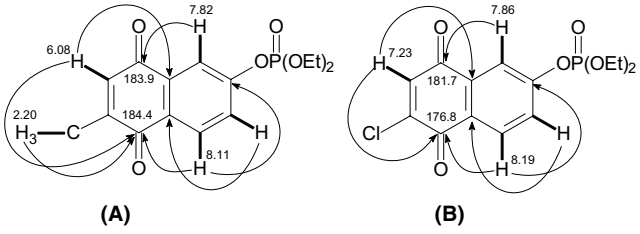
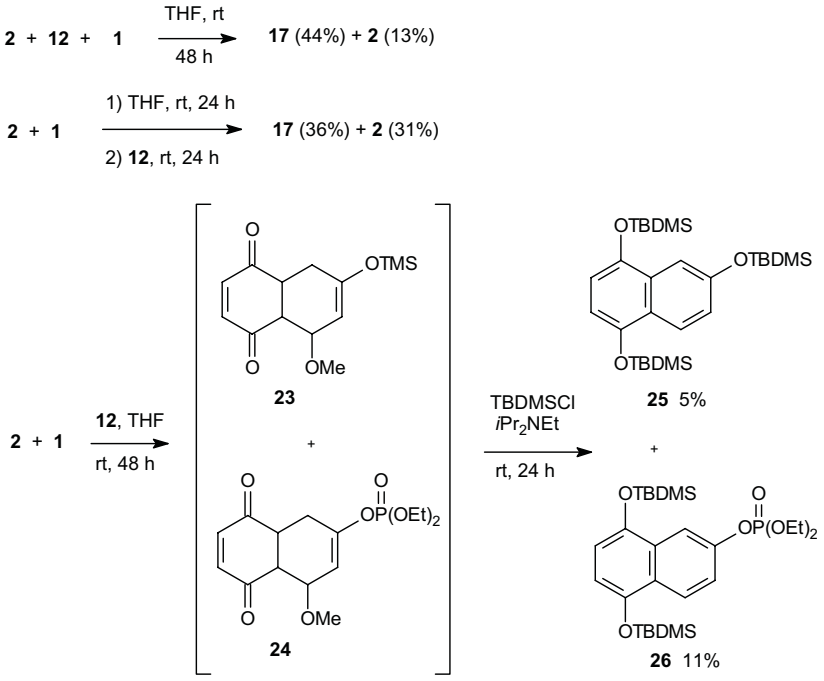


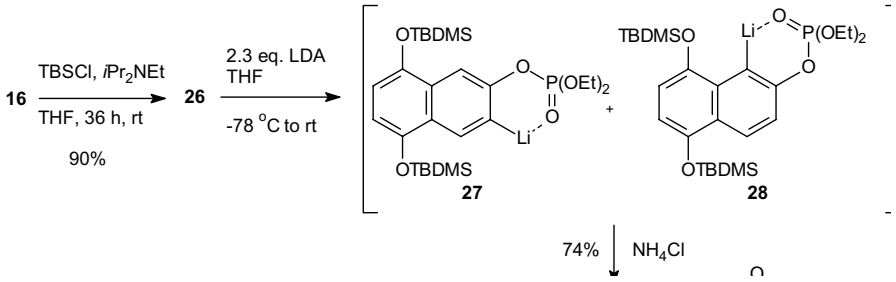
Figure 1. Key HMQC (▬) and HMBC (↷) correlations for compounds **18** (A) and **19** (B).

To gauge the relative reactivity of phosphate diene **2**, competition experiments were attempted with the silyloxy diene **1**. Initially, a mixture of dienes **2** (1.0 mmol) and **1** (1.0 mmol) in THF was treated with 1 equiv of benzoquinone. After column chromatography of the reaction mixture, the phosphate **17** was obtained as the major product (44%) from this reaction and the starting material **2** was recovered in 13% yield. In a second experiment, an equimolar mixture of phosphate diene **2** and diene **1** was stirred for 24 h and then treated with 1 equiv of benzoquinone in THF at rt for an additional 24 h. After column chromatography, the phosphate **17** was again isolated as the major product (Scheme 3).

Danishefsky reported that the attempted isolation of compound **23** was unsuccessful because of its tendency to eliminate methanol and aromatize, and in their studies the reaction mixture was treated with acetic anhydride and pyridine to avoid oxidation and generate more stable acetylated products.[2] When a similar work-up with TBDMSCl and diisopropylethylamine was employed after a competition reaction with equimolar diene **2**, diene **1**, and quinone **12**, the predominant product was the aryl phosphate **26**. In this case, after column chromatography compound **26** was isolated as the major product although in just 11% yield. Compound **25** was also isolated but in just 5% yield. Taken together, these experiments suggest that the phosphate diene **2** is comparable in its stability and reactivity to the better known silyloxy diene **1**, at least with benzoquinone as the dienophile.



Scheme 3. Competition experiments.



Scheme 4. Rearrangement of an aryl phosphate.

One attractive feature of the phosphate diene cycloadditions with quinones is that the aromatic product contains an aryl phosphate originating in the diene moiety. As a result, it is positioned regiospecifically in the B-ring of the cycloadduct, and it may be useful for further elaboration of this product. As shown in Scheme 4, treatment of the TBDMS-protected compound **26** with LDA generated compounds **29** and **30** through a rearrangement that involved disconnection of an oxygen–phosphorus bond and the formation of a carbon–phosphorus bond.[10–17] Two regioisomeric intermediates (**27** and **28**) may be formed upon treatment of the starting phosphate with a strong lithium base. Rearrangement generates two phosphonates and protonation affords the isolated products **29** and **30**. Analysis of the initial reaction mixture by ^{31}P NMR spectroscopy revealed two signals, at 26.2 and 25.6 ppm in an 11:1 ratio. The major product was isolated and characterized as compound **29**. In the ^{1}H NMR spectrum, doublets were observed at δ 8.30 (with $^{3}J_{P-H} = 16.8$ Hz) and at δ 7.5 (with $^{4}J_{P-H} = 6.5$ Hz), attributable to H-5 and H-8. Therefore, in this case, lithiation of compound **26** probably took place at both the C-5 and C-7 positions, resulting in 1,3 P–O to P–C migration to either of the two metalated positions and leading to a mixture of phosphonates **29**[18] and **30**. Although rearrangement of silyl groups following *ortho* metalation might occur,[19] in this case no products of a silyl rearrangement were detectable.

In summary, cycloaddition reactions of the phosphate dienes **2** and **3** can be used to generate aromatic phos-

phates. Phosphate diene **2** shows reactivity, stability, and regioselectivity comparable to the corresponding silyloxy diene, and offers a potential advantage in direct introduction of an aryl phosphate group that may be useful for further elaboration of the cycloadduct. Treatment of the aryl phosphate **26** with LDA results in a phosphate–phosphonate rearrangement with good regioselectivity and no evidence of aryl silane formation. These phosphonates would be more difficult to obtain from cycloadditions with the better known silyloxy dienes, and reflect the potential value of phosphate diene cycloadditions for direct incorporation of reactive functionality in the cycloadducts.

Acknowledgement

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8. For compound **16**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.05 (d, $J = 9.2$ Hz, 1H), 7.80 (s, 1H), 7.17 (ddd, $J = 9.2$, 1.2 Hz, $J_{HP} = 1.2$ Hz, 1H), 6.59 (dd, $J = 8.1$, 1.2 Hz, 1H), 6.53 (dd, $J = 8.1$, 1.2 Hz, 1H), 4.22–4.12 (m, 4H), 1.28 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 149.1 (d, $J_{CP} = 7.2$ Hz), 147.3, 146.8, 127.6, 125.6, 124.7, 119.5 (d, $J_{CP} = 5.1$ Hz), 112.3 (d, $J_{CP} = 4.8$ Hz), 110.1, 108.7, 66.2 (d, $J_{CP} = 6.5$ Hz, 2C), 16.4 (d, $J_{CP} = 6.5$ Hz, 2C); ^{31}P NMR (CD_3OD) δ −3.60. Anal. Calcd for $C_{14}H_{17}O_6P$: C, 53.85; H, 5.49. Found: C, 54.12; H, 5.50.
9. For compound **17**: ^{1}H NMR (600 MHz, CD_3OD) δ 8.10 (d, $J = 8.5$ Hz, 1H), 7.85 (dd, $J = 2.4$ Hz, $J_{HP} = 0.7$ Hz, 1H), 7.62 (ddd, $J = 8.5$, 2.5 Hz, $J_{HP} = 0.9$ Hz, 1H), 7.01 (d, $J = 10.3$ Hz, 1H), 6.98 (d, $J = 10.3$ Hz, 1H), 4.32–4.24 (m, 4H), 1.40 (dt, $J = 7.1$ Hz, $J_{HP} = 1.0$ Hz, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 185.1, 184.9, 156.0 (d, $J_{CP} = 6.4$ Hz), 139.8, 139.6, 135.1, 130.2, 129.9, 126.4 (d, $J_{CP} = 4.7$ Hz), 117.9 (d, $J_{CP} = 4.9$ Hz), 66.7 (d, $J_{CP} = 6.3$ Hz, 2C), 16.3 (d, $J_{CP} = 6.8$ Hz, 2C); ^{31}P NMR δ −6.65; Anal. Calcd for $C_{14}H_{15}O_6P$: C, 54.20; H, 4.87. Found: C, 54.45; H, 5.10.
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18. For compound **29**: ^{1}H NMR (300 MHz, CD_3OD) δ 9.94 (d, $J_{HP} = 0.9$ Hz, 1H), 8.30 (d, $J_{HP} = 16.8$ Hz, 1H), 7.52 (d, $J_{HP} = 6.5$ Hz, 1H), 6.70 (d, $J = 8.1$ Hz, 1H), 6.50 (d, $J = 8.1$ Hz, 1H), 4.25–4.12 (m, 2H), 4.11–3.98 (m, 2H), 1.31 (dt, $J = 7.0$ Hz, $J_{HP} = 0.6$ Hz, 6H), 1.06 (s, 9H), 105 (s, 9H), 0.23 (s, 6H), 0.22 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 157.2 (d, $J_{CP} = 7.6$ Hz), 146.4, 144.7, 133.5 (d, $J_{CP} = 2.6$ Hz), 129.7 (d, $J_{CP} = 6.9$ Hz) 123.2, 123.0, 115.0, 112.6, 110.1 (d, $J_{CP} = 10.9$ Hz), 63.1 (d, $J_{CP} = 4.7$ Hz, 2C), 26.2 (3C), 26.1 (3C), 18.7, 18.6, 16.4 (d, $J_{CP} = 6.3$ Hz, 2C), −4.0 (2C), −4.1 (2C); ^{31}P NMR δ +26.2. Anal. Calcd for $C_{26}H_{45}O_6PSi_2$: C, 57.75; H, 8.39. Found: C, 57.93; H, 8.62.
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