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Highly Selective 1,4- and 1,6-Addition of P(O)–H Compounds to *p*-Quinones: A Divergent Method for the Synthesis of *C*- and *O*-Phosphoryl Hydroquinone Derivatives

Biquan Xiong,[a, b] Ruwei Shen,[c] Midori Goto,[b] Shuang-Feng Yin,*[a] and Li-Biao Han*[a, b]

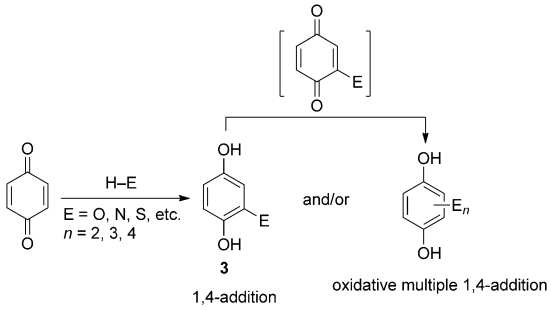
Abstract: The reaction of P(O)–H compounds with *p*-quinones could proceed through either 1,4- or 1,6-addition pathways by employing different additives to selectively give the corresponding C- and O-phosphoryl hydroquinone derivatives in good yields. Oxidative double 1,4-addition of P(O)–H compounds to *p*-quinones was also achieved by tuning the solvent, affording a facile synthesis of bis-substituted hydroquinones with phosphorus functionality. Further studies on these reactions by using optically active H-phosphinates showed that all addition reactions took place stereospecifically with retention of configuration at the phosphorus center. The findings lead to the establishment of a divergent method for the synthesis of C- and O-phosphoryl hydroquinone derivatives from easily available P(O)–H compounds.

Keywords: nucleophilic addition · enantioselectivity · phosphorus · quinones

Introduction

Hydroquinone compounds bearing heteroatom functionalities form a class of valuable compounds with wide applications.[1–8] Many of them serve as important intermediates from which to access molecules with advanced structures by further manipulating the heteroatomic group through synthetic chemistry.[2,3] Some hydroquinones with heteroatom functionalities are used as reagents in medical research, showing a variety of biological activities in aspects related to antitumor,[4] HIV transcriptase inhibition, and immunomodulation.[5] Furthermore, they are also applied in material science and the petroleum industry.[6–8] Thus, an efficient and selective synthesis of these compounds is of importance and is highly desired.

As depicted in Scheme 1, the addition reaction of H–E (E = N, O, S, P etc.) to *p*-benzoquinone may represent one of the most facile and efficient ways to prepare hydroquinones substituted with a heteroatomic group.[9–11] Thus, the reaction of a heteroatomic nucleophile with *p*-benzoquinone gives 2-monosubstituted hydroquinone **3** through normal nucleophilic 1,4-addition. Depending on the properties of E–H, the redox potential of **3**, as well as the reaction conditions, the initially formed hydroquinone **3** could be oxidized and undergo further nucleophilic addition to give multisubstituted hydroquinones.[11i] Theoretically, this addition may allow the introduction of up to four heteroatom functionalities to *p*-benzoquinone, affording a fully substituted hydroquinone that is not easily fabricated by other methods.



Scheme 1. Traditional 1,4-addition of nucleophiles to *p*-quinones.

The reactions of *p*-quinones with E–H (E = O, S, N) compounds were investigated in considerable detail. The reac-

[a] B. Xiong, S.-F. Yin, L.-B. Han
Department of Chemistry
College of Chemistry and Chemical Engineering
Hunan University
Changsha, 410082 (P. R. China)
Fax: (+86) 731-88821310
E-mail: sf_yin@hnu.edu.cn

[b] B. Xiong, M. Goto, L.-B. Han
National Institute of Advanced Industrial Science and Technology (AIST)
Tsukuba, Ibaraki 305-8565 (Japan)
E-mail: libiao-han@aist.go.jp

[c] R. Shen
State Key Laboratory of Materials-Oriented Chemical Engineering
College of Chemistry and Chemical Engineering
Nanjing University of Technology
Nanjing 210009 (P. R. China)

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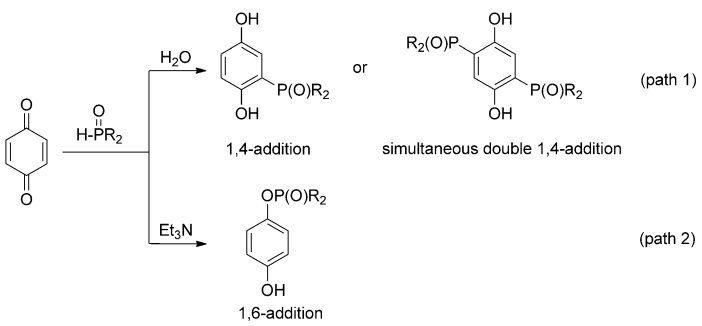
tion of *p*-quinones with alcohols resulted in the formation of the corresponding 4-alkoxy phenols, as reported by Mitsunobu in 1968.[9b] Yamaoka initiated a study on the reaction of *p*-quinone with amine in 1971 and found that mono- and bis-substituted hydroquinones could be produced from the reactions of *p*-quinone with primary and secondary amines in alcohol solvents.[10m] The addition of thiols to *p*-benzoquinone has been discussed in detail by Snell and Weissberger; they found that by using an excess of *p*-quinone, the monosubstituted product could be formed with satisfactory yields in alcohol solvent without addition of a catalyst.[11k] Yasuo Abe further found that the adducts of S–H type compounds could be further oxidized by *p*-quinones, thus obtaining multisubstituted hydroquinones.[11j] Compared with O, N, and S nucleophiles, the number of investigations on the addition reaction of P(O)–H compounds to *p*-quinones is rather limited. A brief study on the use of dialkylphosphites was reported by Levin and Davydochkina, but the procedure used for the preparation of hydroquinone derivatives bearing organophosphorus functionality is tedious and the selectivity and yield were rather low.[12] Consequently, although hydroquinones with organophosphorus functionality are important targets in organic synthesis, medicinal chemistry, and material science, the most frequently employed method for their preparation is still achieved through treatment of $(RO)_2P(O)Cl$ with phenols,[13] and then rearrangement by reaction with organometallic reagents, for example, *n*BuLi or lithium diisoprpylamine (LDA).[14] It is apparent that the approach is time-consuming, limited in terms of generality, and suffers from a lack of tolerance towards functional groups.

In this paper, we disclose the details of our findings on the reaction of P(O)–H compounds with *p*-quinones, providing a divergent method for the synthesis of both C- and O-phosphoryl-substituted hydroquinone derivatives (Scheme 2). During our ongoing project on the preparation of organophosphorus compounds by employing relatively easily accessible P(O)–H compounds,[12] we observed water-promoted 1,4-addition and oxidative double 1,4-addition of P(O)–H compounds to *p*-quinones, affording a facile synthesis of mono- and bis-substituted hydroquinones with phosphorus functionality (Scheme 2, path 1). A mechanistic study showed that this oxidative double 1,4-addition of P(O)–H compounds to *p*-quinones proceeded through a simultaneous double 1,4-addition and subsequent oxidation process, rather than the generally accepted stepwise 1,4-addition/oxidation sequence (see below). Furthermore, when Et_3N was used as an additive, the reaction of P(O)–H compounds with *p*-quinones proceeded through a 1,6-addition route, affording the O-phosphoryl-substituted hydroquinone derivatives (Scheme 2, path 2). The disclosed reactions can all be used for the preparation of optically active organophosphorus hydroquinones from chiral H-phosphinates with retention of configuration at the phosphorus center.

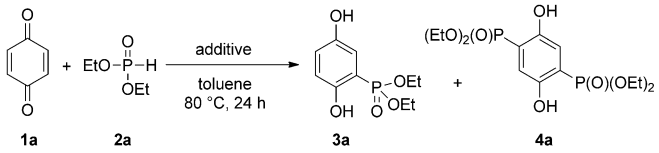


Scheme 2. Outline of our present work.

Results and Discussion

Water-promoted selective 1,4-addition of P(O)–H compounds to *p*-quinones; selective synthesis of C-phosphoryl hydroquinone derivatives: At the outset, we examined the reaction of *p*-benzoquinone (**1a**) and diethyl phosphonate (**2a**) conducted in toluene with a concentration of 0.5 M at 80 °C; the outcome was the formation of diethyl 2,5-dihydroxyphenylphosphonate (**3a**) in 46% yield together with bis-substituted product, tetraethyl 2,5-dihydroxy-1,4-phenylenediphosphonate (**4a**) in 11.5% yield. Thus, besides the 1,4-addition to give **3a** as major product, a double 1,4-addition and oxidation sequence occurred to produce the by-product **4a**. We next concentrated our efforts on optimizing the reaction. As shown in Table 1, a change in the concentration of substrates did not lead to any improvement. Although a higher yield was obtained when the reaction was conducted at a concentration of 1.0 M, the product selectivity declined. The reaction became rather sluggish and the yield of **3a** was poor after 24 h when the reaction was conducted at low substrate concentration.

Table 1. Effects of additives on the 1,4-addition reaction of diethyl phosphonate to 1,4-benzoquinone.[a]



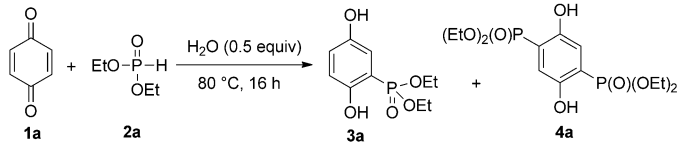
Entry	Conc. [M]	Additive [equiv]	Yield of **3a** [%][b]	Ratio of **3a**/**4a**[b]
1	0.1	–	13	86:14
2	0.3	–	28	83:17
3	0.5	–	46	80:20
4	1.0	–	59	77:23
5	0.5	AcOH (0.2)	68	85:15
6	0.5	AcOH (0.5)	64	87:13
7	0.5	AcOH (1.0)	61	88:12
8	0.5	HCOOH (0.2)	70	88:12
9	0.5	H_2O (0.2)	80	91:9
10	0.5	H_2O (0.5)	85	94:6
11	0.5	H_2O (1.0)	84	91:9

[a] Reaction conditions: 1,4-benzoquinone (0.5 mmol), diethyl phosphonate (0.5 mmol), additive, toluene, N_2, 80 °C, 24 h. [b] Yields and selectivity were determined by GC analysis.

Interestingly, both product yield and selectivity were improved when a trace amount of protic solvent was added to the reaction system. In the presence of 0.5 equivalent of HOAc, the reaction of **1a** with **2a** gave **3a** in 64% yield and the selectivity of **3a**/**4a** was improved to 87:13. The presence of formic acid also gave good results, and the 1,4-addition product **3a** was formed in 70% yield with **3a**/**4a** selectivity of 88:12. Surprisingly, we observed that the addition of a small amount of water improved the outcome of the reaction; thus, the addition of 0.2 equivalent of water led to 80% yield and 91% selectivity for **3a**. When the reaction was performed in toluene at 80°C in the presence of 0.5 equivalent of water, **3a** was formed in 85% yield and the byproduct **4a** was produced in only 5% yield (Selectivity: **3a**/**4a** = 94:6). Adjusting the amount of water to 1.0 equivalent caused a slight decrease in both the yield of **3a** and the selectivity.

The solvents used also had a significant influence on the yield of **3a** and the selectivity in the water-promoted 1,4-addition reaction of P(O)–H compounds to *p*-quinones. As demonstrated in Table 2, reactions conducted in solvents including toluene, benzene, hexane, diphenyl ether, and methyl phenyl ether all showed a preference towards the formation of 1,4-addition product **3a**. The use of polar solvents such as *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), however, gave a reverse selectivity. Thus, the reactions in toluene, benzene, and hexane produced **3a** in good to moderate yield, showing a selectivity of 94, 92, and 78%, respectively, whereas the employment of DMF and DMSO gave **4a** as the main product. Such a phenomenon led to the establishment of a simple and direct way to access bisphosphoryl-substituted hydroquinones (see below). Accordingly, we chose 0.5 mmol of *p*-quinone, 0.5 mmol of P(O)–H compounds, 0.5 equivalent of water as additive, and 1 mL of toluene as the solvent at 80°C under N_2 atmosphere as the optimized conditions.

Table 2. Effects of solvents on diethyl phosphonate 1,4-addition to *p*-benzoquinone.[a]



Entry	Solvent	Yield of **3a** [%][b]	Ratio of **3a**/**4a**[b]
1	toluene	85	94:6
2	benzene	83	92:8
3	EtOAc	45	82:18
4	acetone	19	80:20
5	dioxane	21	79:21
6	hexane	71	78:22
7	DMF	5	33:67
8	DMSO	10	20:80
9	diphenyl ether	75	90:10
10	methyl phenyl ether	53	64:36
11	no solvent	56	63:37

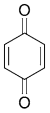
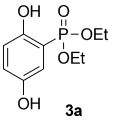
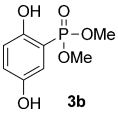
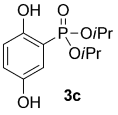
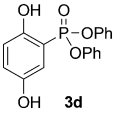
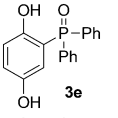
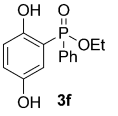
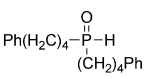
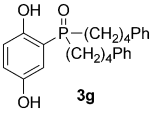
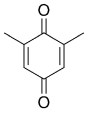
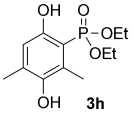
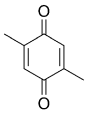
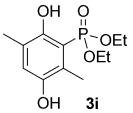
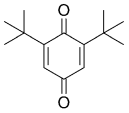
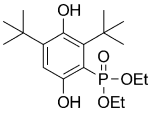
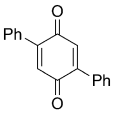
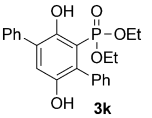
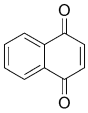
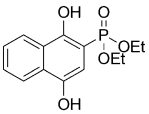
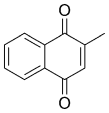
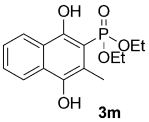
[a] Reaction conditions: 1,4-benzoquinone (0.5 mmol), diethyl phosphonate (0.5 mmol), H_2O (0.25 mmol), solvent (1 mL), N_2 atmosphere, 80°C, 16 h. [b] Yields and selectivity were determined by GC analysis.

As shown in Table 3, the selective 1,4-addition could be applied to a variety of P(O)–H substrates and *p*-quinones. H-phosphonates bearing ethyl and isopropyl groups could be efficiently added to *p*-benzoquinone to afford monosubstituted hydroquinones in high yields. Only a moderate yield was observed when dimethyl phosphonate **2b** was employed in the reaction. On the other hand, diphenyl phosphonate did not give the expected product, possibly due to the tendency of this kind of substrate to undergo hydrolysis.[12d,e] Secondary phosphine oxides such as diphenyl phosphine oxide and bis(4-phenbutyl)phosphine oxide exhibited high reactivity in the reaction and produced the corresponding adducts in 98 and 77% yield, respectively. The reaction of H-phosphinate **2f** also gave the desired product in high yield. A variety of *p*-quinones including 2,5-dimethyl-1,4-benzoquinone, 2,6-dimethyl-1,4-benzoquinone, 2,5-diphenyl-1,4-benzoquinone, and naphthoquinone, were also examined. Whereas the reaction of 2,5-dimethyl-1,4-benzoquinone with **2a** produced the corresponding product in 45% yield, the use of 2,6-dimethyl-1,4-benzoquinone showed an excellent adduct yield. In contrast, only 15% yield of **3j** was obtained from 2,6-di-*tert*-butyl-1,4-benzoquinone due to the high steric hindrance. The reaction of naphthoquinone with **2a** proceeded smoothly to give the desired adduct **3l** in good yield. However, 2-methylnaphthalene-1,4-dione **1g** was inert to this addition and no reaction was observed when **2a** and **1g** were subjected to the reaction under the optimized conditions.

Et_3N-promoted 1,6-addition of P(O)–H compounds to *p*-quinones; selective synthesis of O-phosphoryl hydroquinone derivatives: To our surprise, when we switched the additive from acid (or H_2O) to an organic base (i.e., Et_3N) the reaction took place preferentially through 1,6-addition to give diethyl 4-hydroxyphenyl phosphate (**5a**) as the major product (Table 4). Thus, when the reaction of *p*-benzoquinone (**1a**) with diethyl phosphonate (**2a**) was conducted following a similar procedure in the presence of 10 mol% Et_3N at 80°C in toluene, **5a** was detected (based on GC analysis) in 87% yield with 89% selectivity instead of the expected C-phosphoryl **3a** and **4a** products. Decreasing the reaction temperature led to an increase in both the yield of **5a** and the selectivity. When the reaction was carried out at room temperature (25°C), **5a** was produced in 92% yield with a selectivity of up to 95% after 24 h. We observed that a reduction in the amount of Et_3N from 10 to 1 mol% resulted in a sharp decrease in yield and selectivity of the expected product; further increases in the amount of Et_3N did not lead to any significant improvement. Accordingly, the reaction was further studied in toluene at 25°C using 10 mol% Et_3N as catalyst.

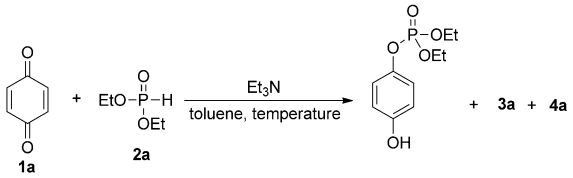
Summarized in Table 5 are the results of the Et_3N-promoted 1,6-addition reaction with *p*-quinones across a variety of P(O)H compounds. The reaction of H-phosphonates **2a**–

Table 3. Water-promoted selective 1,4-addition of P(O)–H compounds to *p*-quinones.[a]

Entry	*p*-Quinone **1**	P(O)–H **2**	Product **3**	Yield [%][c]
1	 **1a**	 **2a**	 **3a**	85
2	**1a**	 **2b**	 **3b**	51
3	**1a**	 **2c**	 **3c**	81
4	**1a**	 **2d**	 **3d**	n.d.
5	**1a**	 **2e**	 **3e**	98
6	**1a**	 **2f**	 **3f**	84
7	**1a**	 **2g**	 **3g**	77
8	 **1b**	**2a**	 **3h**	91
9	 **1c**	**2a**	 **3i**	45
10	 **1d**	**2a**	 **3j**	15
11	 **1e**	**2a**	 **3k**	87[b]
12	 **1f**	**2a**	 **3l**	55
13	 **1g**	**2a**	 **3m**	n.d.

[a] Reaction conditions: 1,4-benzoquinone (1 mmol), P(O)–H (1 mmol), H_2O (0.5 mmol), toluene (2 mL), N_2 atmosphere, 80 °C, overnight. [b] Reaction performed at 110 °C. [c] Isolated yield. n.d. = not determined.

Table 4. Optimization of the 1,6-addition reaction of diethyl phosphonate to 1,4-benzoquinone.[a]



1a 2a

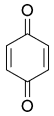
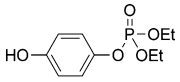
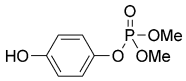
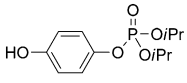
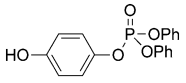
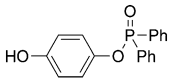
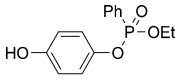
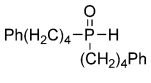
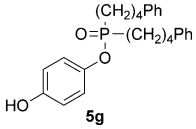
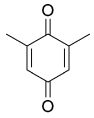
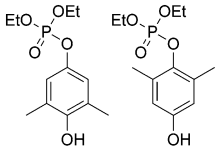
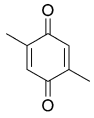
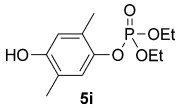
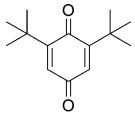
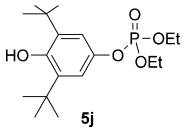
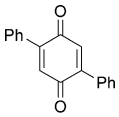
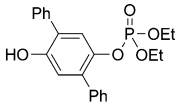
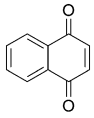
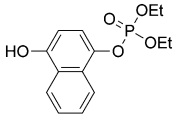
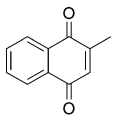
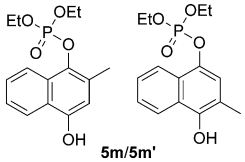
Entry	Et_3N [mol %]	Temp. [°C]	Yield of **5a** [%][c]	Selectivity of **5a** [%][c]
1	10	25	92 (91[d])	97
2[b]	10	40	91	91
3[b]	10	80	87	89
4[b]	10	100	81	88
5	1	25	49	78
6	20	25	88	96
7	50	25	87	94

[a] Reaction conditions: 1,4-benzoquinone (1 mmol), diethyl phosphonate (1 mmol), Et_3N, toluene (1 mL), N_2 atmosphere, RT, overnight. [b] Reaction time: 14 h. [c] Yields and selectivity were determined by GC analysis. [d] Isolated yield.

d with *p*-benzoquinone (**1a**) produced the expected O-phosphoryl hydroquinones in good to excellent yields. When H-phosphinate **2f** was employed, the reaction gave the desired product **5f** in 62% yield. The corresponding adduct **5g** was also obtained from an alkyl secondary phosphine oxide, albeit in a slightly low yield. Nevertheless, the use of diphenyl phosphine oxide unfortunately did not generate the expected product because it was not acidic enough to allow deprotonation and hence this substrate predominantly underwent 1,4-addition, yielding **3e** as the major product. In addition to **1a**, other *p*-quinones including 2,6-bis-substituted and 2,5-bis-substituted 1,4-benzoquinones and 1,4-naphthalenediones could also be employed to produce the O-phosphoryl hydroquinones in good to high yields. Furthermore, the reaction of 2,5-dimethyl-1,4-benzoquinone (**1c**) with **1a** under the optimized conditions produced the expected diethyl 4-hydroxy-2,5-dimethylphenyl phosphate (**5i**) in 93% yield. On the other hand, a mixture of regioisomers **5h** and **5h′** were produced in 91% yield when 2,6-dimethyl-1,4-benzoquinone was employed. It is noteworthy that, in this reaction, the sterically hindered substrate 2,6-di-*tert*-butyl-1,4-benzoquinone (**1d**) regioselectively furnished **5j** in 82% yield. In addition, the reactions of 1,4-naphthalenedione (**1f**) and 2-methylnaphthalene-1,4-dione (**1g**) with **2a** gave the corresponding products in 51 and 77% yield, respectively.

According to previous reports,[12c,f] we propose a mechanism involving a single electron transfer (SET) radical process on the selective 1,6-addition of P(O)H compounds to *p*-quinones (Scheme 3). A catalytic amount of Et_3N is needed to deprotonate the P(O)H compounds to generate the corresponding anion, which are known to be good electron donors. The anion can then react with *p*-quinone through a SET process to give the semiquinone radical anion and a P-centered radical. The anion of the 1,6-addition product is

Table 5. Et_3N-promoted 1,6-addition of P(O)−H compounds to *p*-quinones.[a]

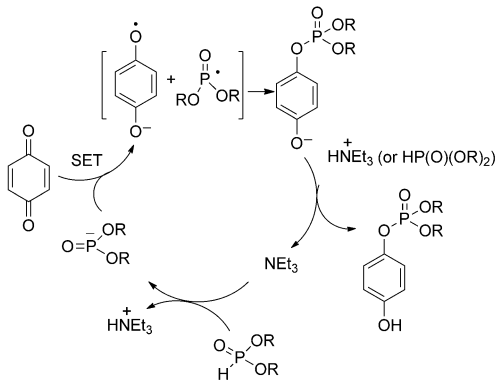
Entry	*p*-Quinone **1**	P(O)−H **2**	Product **3**	Yield [%][c]
1	 **1a**	 **2a**	 **5a**	91
2	**1a**	 **2b**	 **5b**	90
3	**1a**	 **2c**	 **5c**	84
4	**1a**	 **2d**	 **5d**	71
5	**1a**	 **2e**	 **5e**	n.d.
6	**1a**	 **2f**	 **5f**	62
7	**1a**	 **2g**	 **5g**	55
8	 **1b**	**2a**	 **5h/5h'**	91 (65:35)
9	 **1c**	**2a**	 **5i**	93
10	 **1d**	**2a**	 **5j**	82
11	 **1e**	**2a**	 **5k**	69
12	 **1f**	**2a**	 **5l**	51
13	 **1g**	**2a**	 **5m/5m'**	77 (32:68)

[a] Reaction conditions: 1,4-benzoquinone (1 mmol), P(O)-H (1 mmol), Et_3N (0.1 mmol), toluene (1 mL), N_2 atmosphere, RT, overnight. [b] Isolated yield. n.d. = not determined.

subsequently formed, followed by abstraction of a proton from the protonated Et_3N (or the P(O)H compounds) to afford the 1,6-addition product and regeneration of Et_3N.[12c,f]

Oxidative double 1,4-addition of P(O)−H compounds to *p*-quinones; simultaneous double 1,4-addition and subsequent oxidation process: As described above, bis-substituted hydroquinone **4a** is always generated as a byproduct in the 1,4-addition reaction of P(O)−H compounds to *p*-quinones. This phenomenon was also observed by others.[12,13] Surprisingly, we found that **4a** could also be formed preferentially by adjusting the reaction conditions. During the optimization of the 1,4-addition reaction of diethyl phosphonate (**2a**) to *p*-benzoquinone, we found that solvent had a significant impact on the selectivity and formation of **3a** and **4a**. Whereas the use of nonpolar solvents such as toluene and benzene gave an excellent selectivity to produce **3a**, reactions run in polar solvent such as DMSO and DMF favored the formation of bis-substituted product **4a**. When the reaction was conducted in DMSO at 80 °C, **4a** was isolated in a yield up to 72 % (based on diethyl phosphonate **2a**; GC yield: 80 %). Clearly, these findings allow a simple and direct method for the preparation of 2,5-bis-substituted hydroquinones (Table 6).

The formation of product **4** was generally explained by a stepwise pathway involving 1,4-addition and oxidation as shown in Scheme 4.[13b] Accordingly, H-phosphonate **2** first adds to *p*-benzoquinone to produce monosubstituted hydroquinone **3**, which is subsequently oxidized by another equivalent of *p*-benzoquinone to give 2-substituted *p*-benzoquinone **A**. Then, another 1,4-addition of H-phosphonate **2** to **A** takes place, yielding the bis-substituted product **4**. In the whole transformation, *p*-benzoquinone has dual functionality, serving both as substrate and oxidant. Although such a stepwise mechanism can explain the observed experimental results, further study on the mechanism of this reaction by us showed that this might not be the real path. We conducted the reaction of diethyl-2,5-dihydroxyphenyl phosphonate (**3a**) with one equivalent of *p*-benzoquinone (**1a**) under the same reaction conditions. As monitored by GC and ^{31}P NMR analyses, no reaction was observed after heating the mixture for 18 h at 80 °C, hence excluding the possibility of the stepwise mechanism involving an intermediate **A**. Indeed, this result is also consistent with the expectation that **3**, bearing an electron-withdrawing group on the aromatic ring, should have a lower redox potential than hydroquinone,[11i] suggesting that 2-substituted hydroquinone **3** cannot be oxidized by *p*-benzoquinone. Accordingly, we proposed an alternative pathway involving a simul-

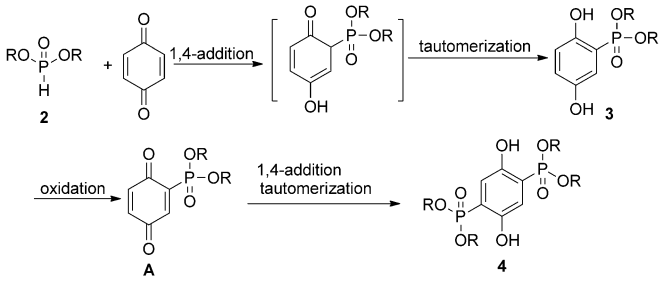


Scheme 3. A proposed SET mechanism for 1,6-addition of P(O)H compounds to *p*-quinones.

Table 6. Oxidative double 1,4-addition of P(O)–H compounds to *p*-quinones to produce bisphosphoryl-substituted hydroquinones.[a]

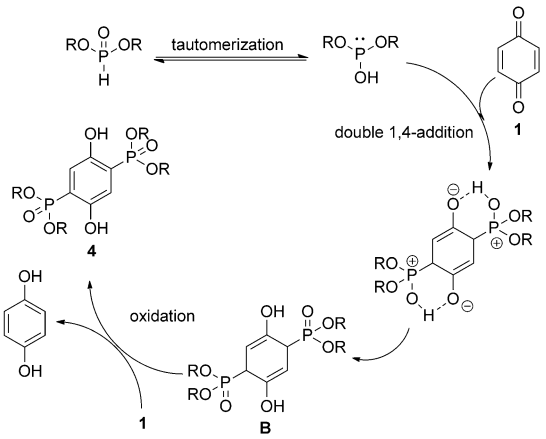
Entry	*p*-Quinone **1**	P(O)–H **2**	Product **4**	Yield [%][b]
1	**1a**	**2a**	**4a**	72
2	**1a**	**2b**	**4b**	22
3	**1a**	**2c**	**4c**	65
4	**1a**	**2e**	**4d**	34

[a] Reaction conditions: 1,4-benzoquinone (1 mmol), P(O)–H (1 mmol), DMSO (1 mL), N_2 atmosphere, 80 °C, overnight. [b] Isolated yield.



Scheme 4. Generally accepted mechanism: a stepwise pathway involving 1,4-addition and oxidation.[12a–b]

taneous double 1,4-addition and subsequent oxidation process to rationalize the reaction. As depicted in Scheme 5, the reaction takes place by the 1,4-addition of two molecules of



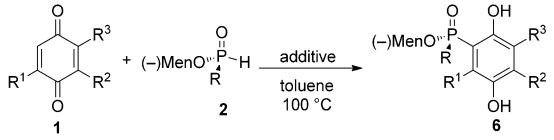
Scheme 5. Our proposed mechanism: simultaneous double 1,4-addition and subsequent oxidation.

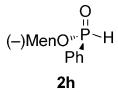
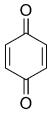
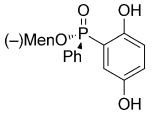
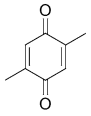
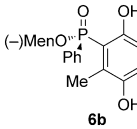
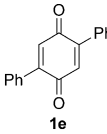
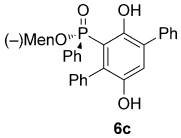
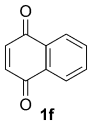
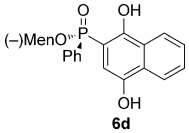
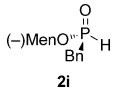
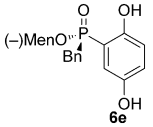
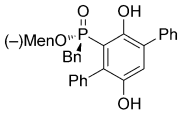
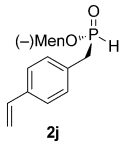
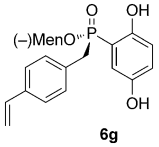
H-phosphonate **2** to *p*-benzoquinone at the 2- and 5-position simultaneously to produce a 2,5-disubstituted cyclohexadiene intermediate **B** followed by its oxidative aromatization by another equivalent of *p*-benzoquinone to give the final product **4**. Similarly, *p*-benzoquinone also acts as both substrate and oxidant.

Stereospecific 1,4- and 1,6-addition of optically active H-phosphinates to quinones; synthesis of hydroquinones bearing chiral P-stereogenic phosphorus functionality: It is worth noting that the current 1,4- and 1,6-addition reactions all proceed highly stereospecifically with retention of configuration at the phosphorus center, thus they can be applied in the preparation of enantiomerically pure *P*-chiral compounds by employing easily accessible optically pure H-phosphinates such as (−)-menthyl phenylphosphinate (R_P)-**2h** (d.r. > 99:1), (−)-menthyl benzylphosphinate (R_P)-**2i** (d.r. > 99:1), and (−)-menthyl-4-vinylbenzylphosphinate (R_P)-**2j** (d.r. > 99:1).[15]

As shown in Table 7, a variety of optically pure monosubstituted hydroquinones with P-chiral phosphoryl functionality were readily generated in moderate to excellent yield by simply heating a mixture of chiral H-phosphinate with *p*-quinone in the presence of 0.5 equivalent of water. *p*-Benzoquinone (**1a**), 2,5-dimethyl-1,4-benzoquinone (**1c**), 2,5-diphenyl-1,4-benzoquinone (**1e**), and naphthoquinone (**1f**) could all be used to react with chiral H-phosphinate (R_P)-**2h**, yielding the corresponding products stereospecifically. Compared with *p*-benzoquinone (**1a**), the reaction of **1c** and **1e** was rather slow under the present reaction conditions. Nevertheless, the expected products were obtained stereospecifically in good yields. The reaction of naphthoquinone with (R_P)-**2h** could afford the corresponding product in yields up to 91% (d.r. > 99:1). In addition to (R_P)-**2h**, (R_P)-(−)-menthyl benzylphosphinate [(R_P)-**2i**] and (R_P)-(−)-menthyl-4-vinylbenzylphosphinate [(R_P)-**2j**] also served as good substrates to produce the corresponding optically active phosphoryl-substituted hydroquinones in good yields (Table 7, entries 5–7). The stereochemistry at phosphorus

Table 7. Stereospecific 1,4-addition of optically active H-phosphinate to *p*-quinones.[a]



Entry	P*(O)–H **2**	*p*-Quinone **1**	Product **6**	Yield [%][d]
1	 **2h**	 **1a**	 **6a**	95
2	**2h**	 **1c**	 **6b**	81
3	**2h**	 **1e**	 **6c**	97[b]
4	**2h**	 **1f**	 **6d**	91[c]
5	 **2i**	**1a**	 **6e**	82
6	**2i**	**1e**	 **6f**	64
7	 **2j**	**1a**	 **6g**	79

[a] Reaction conditions: 1,4-benzoquinone (0.5 mmol), optically active H-phosphinate (0.5 mmol), H_2O (0.25 mmol), toluene (1 mL), N_2 atmosphere, 100 °C, overnight. [b] Reaction performed at 110 °C. [c] Naphthoquinone/H-phosphinate ratio 2:1. [b] Isolated yield.

was confirmed by X-ray analysis of compound **6a**, which unambiguously showed that the reaction proceeded with retention of configuration at the phosphorus center (Figure 1).

Furthermore, phosphoryl-substituted hydroquinone **7** (d.r. > 99:1), bearing two P-stereogenic centers, was also successfully obtained in 45% isolated yield from the reaction of optically active (−)-menthyl phenylphosphinate [(R_P)-**2h**] with *p*-benzoquinone (**1a**) in DMSO through the oxidative double 1,4-addition process (Scheme 6).

Finally, the Et_3N promoted 1,6-addition of optically pure H-phosphinate to *p*-quinones was also found to proceed stereospecifically to afford the O-phosphoryl hydroquinone

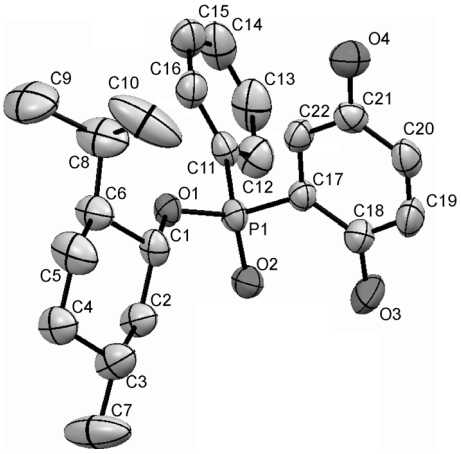
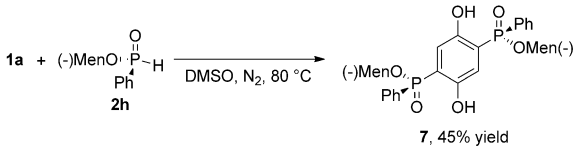
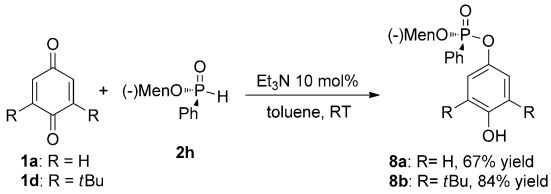


Figure 1. ORTEP drawing of compound (S_P)-**6a**. Hydrogen atoms are omitted for clarity; ellipsoids are drawn at 50% probability. Selected bond lengths [Å] and angles [°]: P1–O1 1.575 (19), P1–O2 1.496 (2), P1–C11 1.790 (3), P1–C17 1.784 (3), C1–O1 1.481 (3), O1-P1-O2 116.11 (11); O2-P1-C17 109.64 (13), O1-P1-C17 109.64 (13), O2-P1-C11 111.70 (13), O1-P1-C11 102.14 (12), C17-P1-C11 109.07 (13), C1-O1-P1 123.87 (17).



Scheme 6. Oxidative double 1,4-addition of optically active H-phosphinate to *p*-quinones to produce bis-P-stereogenic-phosphoryl-substituted hydroquinones.

derivatives with retention of configuration at the phosphorus center. As exemplified in Scheme 7, the reaction of (−)-menthyl phenylphosphinate [(R_P)-**2h**] with 1,4-benzoquinone (**1a**) and 2,6-di-*tert*-butyl 1,4-benzoquinone (**1d**) in the presence of 10 mol% Et_3N took place smoothly at room temperature and yielded the corresponding enantiomerically pure P-chiral compounds (S_P)-**8a** (d.r. > 99:1) and (S_P)-**8b** (d.r. = 95:5) in 67 and 84% yield, respectively. The X-ray structure of (S_P)-**8b** is shown in Figure 2.



Scheme 7. Et_3N-promoted 1,6-addition of optically active phosphinate to *p*-quinones.

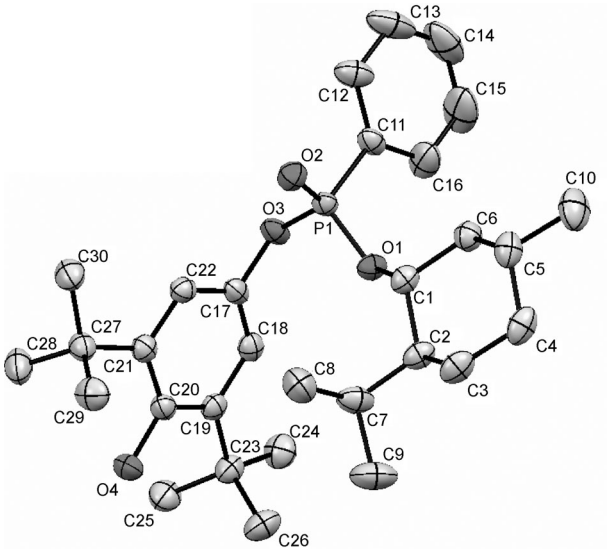


Figure 2. ORTEP drawing of compound (S_P)-**8b**. Hydrogen atoms are omitted for clarity; ellipsoids are drawn at 50% probability. Selected bond lengths [Å] and angles [°]: P1−O1 1.571 (11), P1−O2 1.470 (12), P1−O3 1.589 (11), P1−C11 1.788 (15), C1−O1 1.473 (18); O1-P1-O2 114.95 (6), O1-P1-O3 102.26 (6), O1-P1-C11 108.86 (7), O2-P1-O3 115.67 (7), O2-P1-C11 112.86 (7), C1-O1-P1 112.36 (9), O3-P1-C11 100.84 (7).

Conclusion

We have developed a divergent method for the preparation of C- and O-phosphoryl hydroquinone derivatives from P(O)−H compounds and *p*-quinones through selective 1,4- and 1,6-addition reactions. The method avoids the use of air-sensitive reagents, rendering a simple experimental procedure. It is noteworthy that all the reactions proceed in a highly stereospecific fashion with retention of the configuration at the phosphorus atom, allowing facile access to a variety of optically active organophosphorus compounds from easily available optically active P(O)H compounds. Considering the utility of the resulting compounds, this protocol will have wide application in the construction of biologically active molecules, catalysis ligands, and organophosphorus materials.

Experimental Section

Solvents used for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. ^{1}H (400, 500 MHz), ^{13}C (100, 125 MHz), and ^{31}P (160, 200 MHz) NMR spectra were recorded with a JEOL LA-400 instrument or a JEOL LA-500 instrument, respectively, in $CDCl_3$ or [D_6]DMSO, as specified below. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm), relative to TMS as internal standard; ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ as internal standard, in broad-band decoupled mode. The abbreviations used are as follows: singlet (s), doublet (d), double-doublet (dd), triplet (t), quartet (q), multiplet (m).

Typical procedure for the synthesis of 3a: Diethyl phosphonate (1 mmol) was added to a mixture of *p*-benzoquinone (1 mmol) and H_2O (0.5 mmol) in toluene (1 mL) under a nitrogen atmosphere, and the resulting mixture was stirred at 80 °C for 16 h. GC analysis was used to monitor the reaction, until the signal of *p*-benzoquinone disappeared (indicating the end of the reaction). Removal of the solvent under reduced pressure gave the crude product; pure **3a** was obtained by passing the crude product through a short silica gel column (*n*-hexane/EtOAc). Yield: 0.2092 g (85%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.35 (s, 1H; OH), 7.26 (br, 1H; OH), 6.98–7.26 (m, 1H; Ar), 6.69–6.88 (m, 2H; Ar), 3.97–4.17 (m, 4H; CH_2), 1.28 ppm (t, ^3J(H,P) = 7.2 Hz, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 155.1 (d, ^1J(C,P) = 5.8 Hz; Ar), 149.3 (d, ^1J(C,P) = 17.1 Hz; Ar), 123.7 (d, ^1J(C,P) = 3.8 Hz; Ar), 118.6 (d, ^1J(C,P) = 13.3 Hz; Ar), 116.4 (d, ^1J(C,P) = 6.7 Hz; Ar), 108.4 (d, ^1J(C,P) = 180.1 Hz; CP), 63.1 (d, ^1J(C,P) = 4.7 Hz; CH_2), 16.1 ppm (d, ^1J(C,P) = 6.7 Hz; CH_3); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): δ = 21.9 ppm.

Typical procedure for the synthesis of 4a: *p*-Benzoquinone (1 mmol) and diethyl phosphonate (1 mmol) were dissolved in DMSO (1 mL) under a nitrogen atmosphere and the resulting mixture was stirred at 80 °C for 18 h (^{31}P NMR spectroscopic analysis was used to monitor the reaction). With the disappearance of the ^{31}P signal of diethyl phosphite (indicating the end of the reaction), water was added. Extraction with ethyl acetate and removal of the solvent under reduced pressure gave the crude product; pure **4a** was obtained by passing the crude product through a short silica gel column (*n*-hexane/EtOAc). Yield: 0.1375 g (72%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.62 (s, 2H; OH), 7.10 (t, ^3J(H,H) = 4 Hz, 2H; Ar), 4.03–4.22 (m, 8H; CH_2), 1.35 ppm (t, ^3J(P,H) = 7.2 Hz, 12H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 158.0 (t, ^1J(C,P) = 11.4 Hz; Ar), 127.2 (t, ^1J (C,P) = 5.7 Hz; Ar), 105.9 (dd, ^1J-(C,P_1) = 7.6 Hz, ^1J(C,P_2) = 173.5 Hz; CP), 62.9 (dd, ^1J(C,P_1) = 1.9 Hz, ^1J-(C,P_2) = 0.9 Hz; CH_2), 16.2 ppm (dd, ^1J(C,P_1) = 2.8 Hz, ^1J(C,P_2) = 1 Hz; CH_3); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): δ = 22.32 ppm.

Typical procedure for the synthesis of 5a: Diethyl phosphonate (1 mmol) was added to a mixture of *p*-benzoquinone (1 mmol) and Et_3N (0.1 mmol) in toluene under a nitrogen atmosphere, and the resulting mixture was stirred at RT for 12 h (GC analysis was used to monitor the reaction). When the reaction was complete, removal of the solvent under reduced pressure gave the crude product; pure **5a** was obtained by passing the crude product through a short silica gel column (*n*-hexane/EtOAc). Yield: 0.2239 g (91%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.93 (d, ^3J (H,H) = 8 Hz, 2H; Ar), 6.65 (d, ^3J (H,P) = 8.8 Hz, 2H; Ar), 4.17–4.24 (m, 4H; CH_2), 1.33–1.37 (m, 6H; CH_3), 0.07 ppm (s, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 154.1 (s; Ar), 143.2 (d, ^1J (C,P) = 7.7 Hz; Ar), 120.8 (d, ^1J (C,P) = 4.8 Hz; Ar), 116.4 (s; Ar), 64.8 (d, ^1J (C,P) = 6.7 Hz; CH_2), 16.1 ppm (d, ^1J (C,P) = 6.7 Hz; CH_3); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): δ = −5.82 ppm.

Crystallographic data: CCDC-902258 ((S_P)-**8b**) and 902259 ((S_P)-**6a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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