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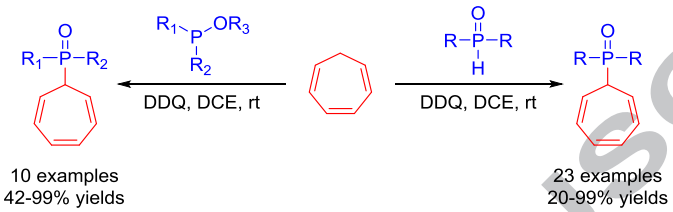

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DDQ-promoted C(sp^3)−H phosphorylation of cycloheptatriene

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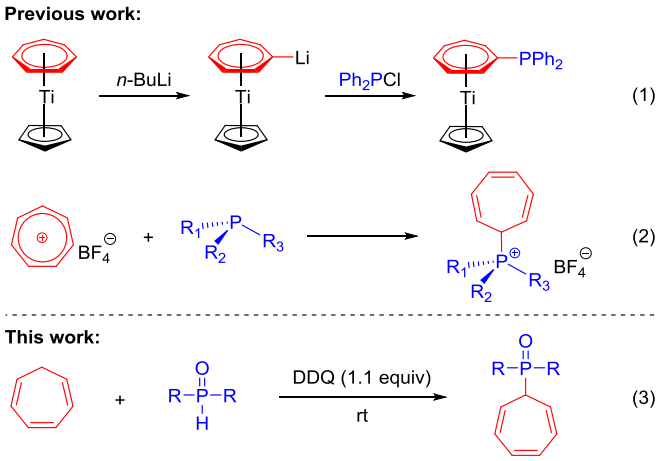
ABSTRACT

An efficient and convenient C(sp^3)−H phosphorylation has been achieved via the DDQ-promoted cross-dehydrogenative coupling between cycloheptatriene and P(O)H compounds at room temperature. This transformation provides a direct synthetic route to the construction of C(sp^3)−P bonds with good functional group compatibility, leading to the formation of cyclohepta-2,4,6-trien-1-ylphosphonates in up to 99% yield.

Organophosphorus compounds are widely used in organic synthesis,[1] materials,[2] bioorganic and medical chemistry,[3] coordination chemistry and catalysis,[4] and flame retardants.[5] As the most important class of ligands in metal-catalyzed reactions, phosphine ligands have attracted much attention because the phosphorous is an effective donor atom with strong σ-donor properties.[6] Compared to arylphosphines, phosphine ligands containing tropylium ($C_7H_7^+$) such as sandwich complexes of the type [(η^7-C_7H_7)M(η^5-C_5H_5)] (M = group 4−6 metals) are less well-documented[7] probably due to the difficulty in their synthesis, although tropyliums are effective ligands for coordination to transition metals.[8] The phosphane-functionalization of the tropylium moiety mainly relies on the lithiation at the cycloheptatrienyl ring (Scheme 1, eqn (1)).[7] However, this method is somewhat limited because alkyllithium reagents and phosphorus chlorides are moisture sensitive and/or environmentally unfriendly. On the other hand, the tropylation of phosphines can be realized by the reactions of tropylium tetrafluoroborate with P(III) compounds to afford cycloheptatriene-phosphonium derivatives (Scheme 1, eqn (2)), while the products such as $[C_7H_7PPh_3]^+[BF_4]^-$ are organic salts.[9] Therefore, the development of a direct and convenient protocol for the preparation of P-tropylated compounds is still a significant issue.

Cycloheptatriene and its related derivatives, which are important moieties in various biologically active compounds,[10] have also been particularly utilized in organic synthesis.[11] Thus, the synthesis of 7-substituted cycloheptatriene derivatives via the reactions of the tropylium ion with various nucleophiles is of importance and interest. Recently, the direct cross-dehydrogenative coupling (CDC) reactions[12] involving P(O)H compounds have received much attention because this strategy represents more straightforward, efficient, and atom-economic to achieve C(sp^3)−H phosphorylation.[13] Base on our recent studies on the construction of P−aryl, P−F, P−O and P−S bonds,[14] we became interested in exploring a direct phosphorylation of various C(sp^3)−H bonds. Most recently, our group developed an efficient C(sp^3)−H phosphorylation of 1,3-diarylpropenes and xanthenes via CDC reactions promoted by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[15] To our knowledge, the C(sp^3)−H phosphorylation of cycloheptatriene has never been reported. Herein, we report a DDQ-promoted direct C(sp^3)−H phosphorylation of cycloheptatriene, leading to the formation of cyclohepta-2,4,6-trien-1-ylphosphonates at room temperature (Scheme 1, eqn (3)).



Scheme 1. Tropylation of organophosphorus compounds.

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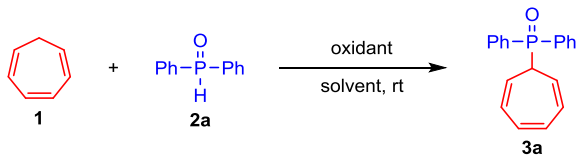
Table 1
Optimization of reaction conditions.[a,b]



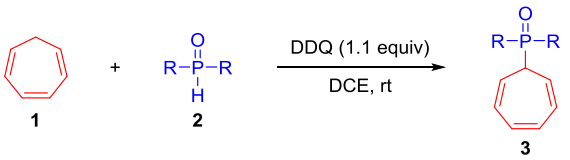
1 2a 3a

Entry	**2a** (equiv)	Oxidant	Solvent	Yield of **3a** (%)
1	2.0	DDQ	CH_3NO_2	91
2	2.0	DDQ	DCM	70
3	2.0	DDQ	THF	93
4	2.0	DDQ	CH_3CN	96
5	2.0	DDQ	DMF	42
6	2.0	DDQ	DMSO	45
7	2.0	DDQ	DCE	99
8	1.5	DDQ	DCE	99
9	1.0	DDQ	DCE	77
10	1.5	PIFA	DCE	80
11	1.5	DTBP	DCE	0
12	1.5	NQ	DCE	0
13	1.5	BQ	DCE	0
14[c]	1.5	DDQ	DCE	quantitative

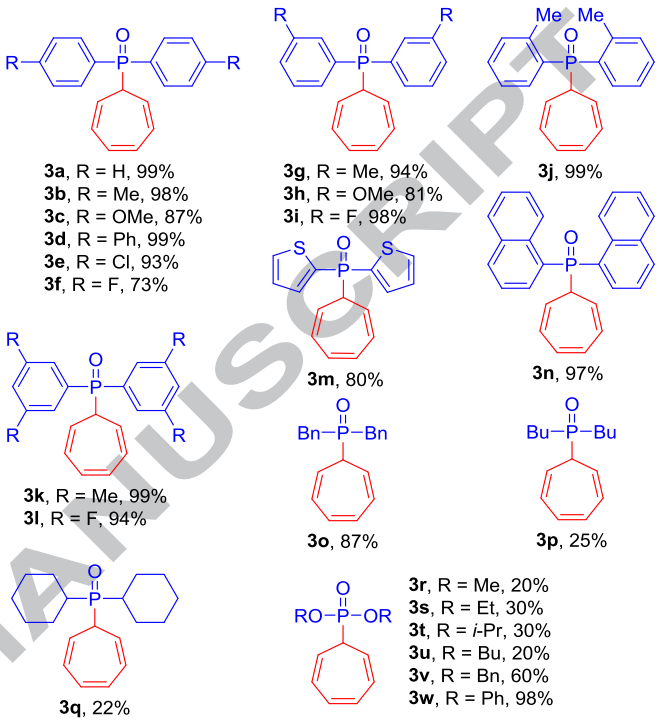
[a] Reaction conditions: **1** (0.2 mmol), **2a**, oxidant (0.3 mmol), anhydrous solvent (2 mL), N_2 atmosphere.
[b] Yield based on **1** was determined by ^1H NMR analysis of crude products using an internal standard.
[c] DDQ (0.22 mmol) was employed.

The reaction conditions were tested by using a model reaction of cycloheptatriene **1** with diphenylphosphine oxide **2a**, and the results were shown in Table 1. First, we carried out the reaction of **1** with **2a** (2.0 equiv) using DDQ (1.5 equiv) as the oxidant in CH_3NO_2 at room temperature under N_2 atmosphere according to our previous work.[15a] To our delight, the reaction proceeded smoothly to afford the desired cyclohepta-2,4,6-trien-1-yldiphenylphosphine oxide **3a** in 91% yield (entry 1). A screen of solvents was then carried out (entries 2−7). DCE (1,2-dichloroethane) was proved to be the optimum solvent, leading to the formation of **3a** in 99% yield (entry 7). When 1.5 equiv of **2a** were employed, **3a** was still obtained in excellent yield (entry 8), while the employment of 1.0 equiv of **2a** significantly decreased the product yield (entry 9). We then turned to screen other synthetically common oxidants (entries 10−13). The use of phenyliodine bis(trifluoroacetate) (PIFA) gave **3a** in 80% yield, while no reaction occurred when using di-*t*-butyl peroxide (DTBP), 1,4-naphthoquinone (NQ) or 1,4-benzoquinone (BQ) as the oxidant. Pleasingly, **3a** was obtained in quantitative yield when near-stoichiometric amounts of DDQ (1.1 equiv) were added (entry 14). Finally, we concluded that the optimized combination for the phosphorylation of cycloheptatriene was to use 1.5 equiv of P(O)H compounds as the phosphorus source, 1.1 equiv of DDQ as the oxidant, DCE as the solvent, and the reaction was set at room temperature under N_2 atmosphere (entry 14).

Table 2
Scope of P(O)H compounds.[a,b]

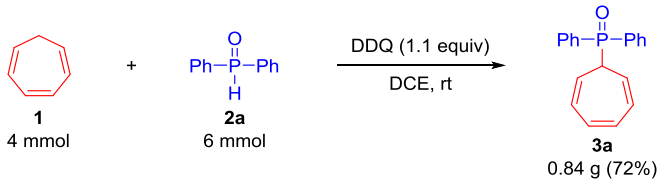


1 2 3



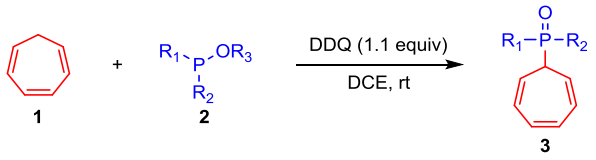
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), DDQ (0.22 mmol), anhydrous DCE (2 mL), room temperature, N_2 atmosphere, 9 h.
[b] Isolated yield based on **1**.

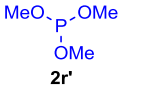
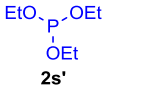
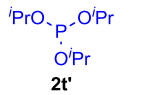
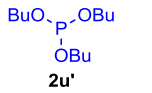
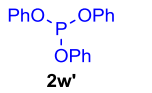
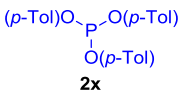
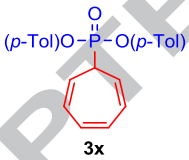
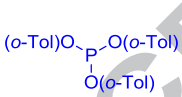
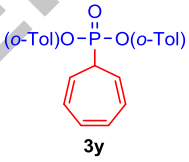
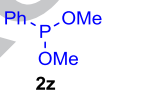
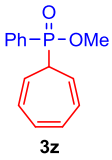
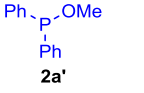
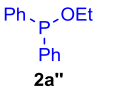
We then set out to explore the generality of the CDC of cycloheptatriene with P(O)H compounds. We first applied the optimized conditions to the coupling of cycloheptatriene **1** with a variety of P(O)H compounds **2**, and the results were illustrated in Table 2. Diarylphosphine oxides bearing different groups such as electron-donating groups (Me, OMe and Ph) and weakly electron-withdrawing groups (Cl and F) at *para*, *meta*, or *ortho* position of aromatic rings, as well as heterocyclic di(thiophen-2-yl)phosphine oxide and sterically hindered di(naphthalen-1-yl)phosphine oxide, were all applicable to the coupling with 73–99% yields (**3a**–**3n**). When dibenzylphosphine oxide was employed, the desired **3o** was isolated in 87% yield, while the reaction of dibutylphosphine oxide or dicyclohexylphosphine oxide with **1** afforded **3p** or **3q** in poor yield probably due to the relatively weak nucleophilicity. We then turned our attention to the reactions of dialkyl/diaryl phosphites. Unfortunately, the coupling of dialkyl phosphites with **1** gave the corresponding **3r**–**3u** in low yields. However, the employment of dibenzyl phosphite and diphenyl phosphite gave the desired **3v** and **3w** in good yields probably owing to the p-π-conjugated system, which may enhance the nucleophilicity. In addition, the scale-up reaction was attempted (Scheme 2). When we increased the scale of the reaction of **1** with **2a** from 0.2 to 4 mmol, **3a** was isolated in 72% yield (0.84 g).



Scheme 2. Scale-up of the phosphorylation reaction.

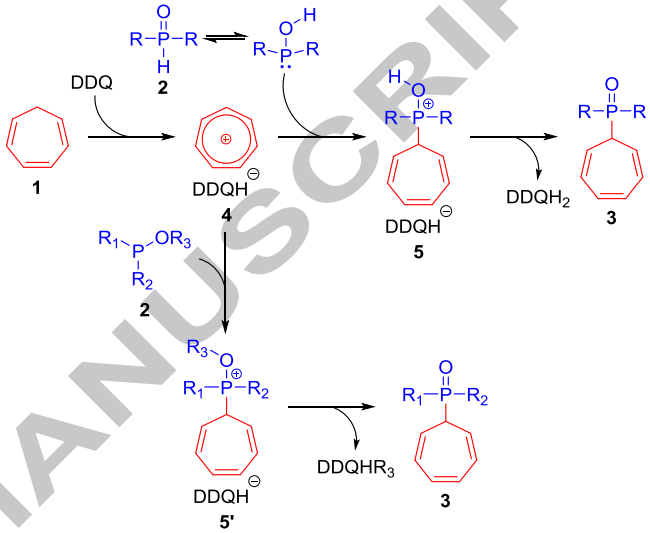
Table 3
Scope of P(III) compounds.[a,b]



Entry	P(III) compound	Product	Yield (%)
1	 **2r'**	**3r**	98
2	 **2s'**	**3s**	97
3	 **2t'**	**3t**	96
4	 **2u'**	**3u**	98
5	 **2w'**	**3w**	99
6	 **2x**	 **3x**	98
7	 **2y**	 **3y**	98
8	 **2z**	 **3z**	45
9	 **2a'**	**3a**	42
10	 **2a''**	**3a**	57

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), DDQ (0.22 mmol), anhydrous DCE (2 mL), room temperature, N_2 atmosphere, 9 h.
[b] Isolated yield based on **1**.

In consideration of significant applications of dialkyl alkylphosphonates in organic synthesis,[1] we then carried out the Michaelis-Arbuzov-type reaction[16] of **1** with the more nucleophilic P(III) compounds (Table 3). Notably, the reactions of trialkyl phosphites or triaryl phosphites with **1** afforded the desired **3r**−**3u** or **3w**−**3y** in excellent yields (entries 1−7). In addition, the cross-coupling of P(III) compounds bearing one or two alkoxy substituents with **1** was attempted. When $PhP(OMe)_2$, Ph_2POMe, or Ph_2POEt was used as the phosphorus nucleophile, the corresponding **3z** and **3a** were isolated in moderate yields (entries 8−10).



Scheme 3. Proposed mechanism.

Based on the above experimental results and our previous work,[15] a plausible reaction mechanism is outlined in Scheme 3. Initially, cycloheptatriene **1** interacts with DDQ to generate a tropylium cation and a DDQH-anion. Then, the less stable P(III) form, which exists with the P(V) form **2** via the tautomerization,[17] attacks the tropylium cation to produce an unstable phosphonium cation **5**. The subsequent deprotonation of **5** generates the cross-coupling product **3** and $DDQH_2$. Similarly, the reaction of tropylium cation **4** with P(III) compound **2** produces a phosphonium cation **5'**, and the subsequent transformation via a pathway of the Michaelis-Arbuzov reaction[16] affords **3**. Notably, DDQ is used not only as the oxidant, but also as the hydrogen acceptor in this reaction.

In summary, we have developed the DDQ-promoted cross-dehydrogenative coupling between cycloheptatriene and P(O)H compounds, providing a convenient protocol for the synthesis of tropyl diarylphosphine oxides. Furthermore, the Michaelis-Arbuzov-type reaction of P(III) compounds affords a facile access to dialkyl/diaryl tropylphosphonates. To the best of our knowledge, this finding is the first example of $C(sp^3)$−H phosphorylation of cycloheptatriene. The good functional group compatibility, high yields, and mild reaction conditions showcase the potential of this approach in chemical synthesis.

Acknowledgments

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Supplementary data

Supplementary data (these data include experimental details, analytical data, ^{1}H, ^{13}C and ^{31}P NMR spectra of compounds **3**) associated with this article can be found, in the online version, at http://...

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Highlights

1. The DDQ-promoted C(sp^3)−H phosphorylation has been achieved.
2. The reactions afford cyclohepta-2,4,6-trien-1-ylphosphonates under mild conditions.
3. The protocol is halogen-, metal-, and strong base-free.