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#### **Graphical abstract**



#### Tributylphosphine Catalyzed Addition of Diphenylphosphine Oxide to Unsubstituted and Substituted Electron-Deficient Alkenes

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#### Abstract

The PBu<sub>3</sub>-catalyzed conjugate addition of diphenylphosphine oxide to unsubstituted and substituted electron-deficient alkenes is reported.  $\beta$ -Substituted  $\alpha$ , $\beta$ -unsaturated esters, *trans*-methyl crotonate and *trans*-methyl cinnamate, known for their reluctance to participate in phosphine-catalyzed transformations, also react well under the developed conditions. Mild reaction conditions, simple workup and the ease of catalyst recovery make the proposed methodology useful for the preparation of functionalized tertiary phosphine oxides. The utility of this method was demonstrated by the gram-scale reactions of diphenylphosphine oxide with electron-deficient alkenes.

*Keywords:* Pudovik reaction, Phospha-Michael addition, Phosphine organocatalysis, X-Ray analysis

### Introduction

Tertiary phosphine oxides represent an important class of organophosphorus compounds with applications in industrial chemistry and the life sciences. The reduction of tertiary phosphine oxides provides convenient access to tertiary phosphines, which are broadly applied in organometallic catalysis and organocatalysis.<sup>1</sup> Due to their hydrolytic, thermal and oxidative stability, tertiary phosphine oxides are versatile ligands for the extraction of transuranic,<sup>2</sup> rare-earth<sup>3</sup> and noble metals;<sup>4</sup> as well as the stabilization of quantum dots and other metal nanoparticles.<sup>5</sup> Furthermore, tertiary phosphine oxides are well-established flame retardants for polymers.<sup>6</sup> Consequently, the development of novel efficient methods for the preparation of tertiary phosphine oxides is highly appealing.

One of the most atom-economical and straightforward approaches for the synthesis of tertiary phosphine oxides is the addition of secondary phosphine oxides to unsaturated species, known as the Pudovik reaction or phospha-Michael addition.<sup>7</sup> Due to the relatively low reactivity of the P(O)-H bond, the direct addition to activated carbon-carbon multiple bonds typically occurs only at high temperature.<sup>8</sup> In order to proceed under milder conditions, the reaction can be catalyzed by organic and inorganic bases such as alkaline alkoxides (e.g. MeONa, EtONa), KOH, Ca(OH)<sub>2</sub>, NaH, *n*-BuLi, Et<sub>2</sub>Zn;<sup>7,9</sup> transition metal salts;<sup>10</sup> or radical initiators such as AIBN.<sup>11</sup> Despite the abundance of examples where tertiary phosphines are used as organocatalysts in Michael-type additions for carboncarbon and carbon-heteroatom bond formation,<sup>12</sup> there exist only a few reports regarding the phosphine-catalyzed Pudovik reaction. Recently, Han and coworkers introduced PMe<sub>3</sub> as an efficient and easily removed catalyst for the addition of dialkyl phosphites, alkyl H-phosphinates and secondary phosphine oxides to electron-deficient alkenes.<sup>13</sup> Our group, as well as Kim and co-workers, developed an efficient PBu<sub>3</sub>-catalyzed Pudovik reaction, that can be performed without a protective inert atmosphere and easy catalyst recovery.<sup>14</sup> The scope of this reaction was examined with several electron-deficient alkenes, and it was noted that best yields and shortest reaction times were achieved when the concentration of PBu<sub>3</sub> was varied with respect to the nature of unsaturated reagent (typically, 5-50 mol% of the catalyst were required).<sup>14b,c</sup>

However, secondary phosphine oxides have not been tested for the  $PBu_3$ -catalyzed P(O)–H bond addition reaction, which stimulated us to explore the scope of this reaction using diphenylphosphine oxide as a substrate.

#### **Results and Discussion**

Initially, the model reaction of diphenylphosphine oxide with methyl methacrylate in the presence of PBu<sub>3</sub> was examined under the conditions developed previously for the reaction using dialkyl phosphites as substrates.<sup>14b,c</sup>  $\alpha$ -Substituted methyl methacrylate was examined first, since due to the relatively low reactivity of this alkene in phosphine-catalyzed transformations, the synthetic outcome depends significantly on small variations of the reaction conditions. MeCN was used as a solvent, which facilitates the P(O)–H bond addition.<sup>14,15</sup> We were pleased to find that the application of PBu<sub>3</sub> (50 mol%) in MeCN at room temperature afforded the anticipated product **1a** in 96% yield after 2 h (Table 1, entry 1). This result was superior to that obtained previously for the related reaction of dimethyl- and diethyl phosphites, where the yields were limited to 75% and 78%, respectively.<sup>14b</sup> When lower concentrations of the catalyst were used, the yield of **1a** decreased dramatically (Table 1, entries 2, 3). With less nucleophilic

PPh<sub>3</sub>, the reaction did not proceed (Table 1, entry 4). For this reason, reactions with other electron-deficient alkenes were performed using the conditions optimized for PBu<sub>3</sub>-catalyzed addition of dialkyl phosphites. Various functional groups (ester, nitrile, amide) were tolerated under these reaction conditions (Table 1, entries 5-8). As a general trend, the catalyst loading was increased as: (i) the electrophilicity of the alkene decreased (*cf.* methyl acrylate and acrylonitrile with acrylamide, Table 1, entries 5, 7, 8); (ii) the electron-donating effect of a substituent at the  $\alpha$ -carbon atom increased (*cf.* methyl methacrylate with dimethyl itaconate, Table 1, entries 1, 6). These data correlate well with the rate of addition of tertiary phosphines to unsaturated species as determined from kinetic measurements.<sup>16</sup>





		- 1	2				
Entry	$PR_3 (mol\%)$	R	$\mathbf{R}^2$	EWG	Product	Time	Yield <b>1</b>
						(h)	$(\%)^{b}$
1	PBu <sub>3</sub> (50)	Н	Me	CO <sub>2</sub> Me	1a	2	96
2	PBu <sub>3</sub> (30)	Н	Me	CO <sub>2</sub> Me	1a	4	70
3	PBu <sub>3</sub> (10)	Η	Me	CO <sub>2</sub> Me	<b>1a</b>	4	<5
4	PPh <sub>3</sub> (50)	Η	Me	CO <sub>2</sub> Me	1a	48	0
5	$PBu_3(5)$	Η	Н	CO <sub>2</sub> Me	1b	0.5	90
6	PBu <sub>3</sub> (30)	Η	CH <sub>2</sub> CO <sub>2</sub> Me	CO <sub>2</sub> Me	1c	1	95
7	$PBu_{3}(5)$	Η	Н	CN	1d	0.5	79
8	PBu <sub>3</sub> (20)	Η	Н	CONH <sub>2</sub>	<b>1e</b>	1	91
9	PBu <sub>3</sub> (50)	Me	Н	CO <sub>2</sub> Me	<b>1f</b>	12	77
10	PBu <sub>3</sub> (50)	Me	Н	CO <sub>2</sub> Me	<b>1f</b>	24	77
11	PBu <sub>3</sub> (100)	Me	Н	CO <sub>2</sub> Me	<b>1f</b>	8	77
12	PBu <sub>3</sub> (100)	Ph	Н	CO <sub>2</sub> Me	1g	48	68
0							

<sup>&</sup>lt;sup>a</sup>Reagents and conditions: diphenylphosphine oxide (5 mmol), alkene (5 mmol), PR<sub>3</sub> (5-100 mol%), MeCN (15 mL). <sup>b</sup>Isolated yield.

The sequence of reagents addition was found to be crucial to the chemoselective reactions of diphenylphosphine oxide with methyl acrylate and acrylonitrile under  $PBu_3$  catalysis. Tertiary phosphine oxides **1b** and **1d** were the sole products, if the alkene was added slowly (dropwise) to the mixture of

diphenylphosphine oxide with PBu<sub>3</sub> in MeCN. However, when PBu<sub>3</sub> was added to the equimolar mixture of diphenylphosphine oxide with methyl acrylate (or acrylonitrile) in MeCN, by-product 2 (<10%) could be detected by <sup>31</sup>P NMR spectroscopy of the crude reaction mixture. Evidently, product 2 could result from phosphine-catalyzed dimerization of the activated alkene (Rauhut-Currier reaction)<sup>17</sup> followed by the addition of diphenylphosphine oxide to the newly formed alkene **3** (Scheme 1). These side reactions can be successfully circumvented by lowering the concentration of the alkene in the reaction mixture. Notably, PBu<sub>3</sub> is less prone to form 1:2 adducts **2** than PMe<sub>3</sub>.<sup>13c</sup>



Scheme 1. Dimerization of electron-deficient alkenes in the presence of  $PBu_3$  and subsequent phosphine-catalyzed addition of diphenylphosphine oxide to alkene 3

Noting that diphenylphosphine oxide possessed higher reactivity in the PBu<sub>3</sub>-catalyzed addition to electron-deficient alkenes than the simpler dialkyl phosphites, we directed our efforts to broaden the reaction scope using  $\beta$ substituted activated alkenes. All previous attempts to perform such additions in the presence of tertiary phosphines using dialkyl phosphites and alkyl Hphosphinates as substrates were unsuccessful even under harsh reaction conditions.<sup>14b</sup> The inertness of  $\beta$ -substituted activated alkenes in phosphinecatalyzed reactions is ubiquitous and generally explained by slow addition of tertiary phosphines to these substrates due to steric hindrance of the terminal carbon atom.<sup>17</sup> To our delight, the PBu<sub>3</sub> (50 mol%) catalyzed addition of diphenylphosphine oxide to *trans*-methyl crotonate at room temperature gave the corresponding product 1f in 77% yield after 12 h (Table 1, entry 9). Prolonged reaction times had no effect on the yield (Table 1, entry 10). Using PBu<sub>3</sub> (100 mol%), the reaction could be accelerated and gave similar results (Table 1, entry 11). *trans*-Methyl cinnamate bearing a more bulky phenyl group at the  $\beta$ -carbon atom, also reacted with diphenylphosphine oxide in the presence of PBu<sub>3</sub> (100 mol%) to give the desired product 1g in a synthetically useful 68% yield after 72 h (Table 1, entry 12). The ability of  $PBu_3$  to catalyze the addition of secondary phosphine oxides to β-substituted activated alkenes under mild conditions is quite remarkable, since these reactions typically require more forcing conditions.

The proposed methodology performed well for gram-scale synthesis of tertiary phosphine oxides **1**. Approximately 80-90% of PBu<sub>3</sub> could be recovered from the reaction mixture by extraction with *n*-pentane followed by vacuum distillation; only minimal oxidation of the catalyst was observed by <sup>31</sup>P NMR for the reactions carried out in air. In contrast to the reactions of dialkyl phosphites, no noticeable heat evolution was detected during the PBu<sub>3</sub>-catalyzed addition of diphenylphosphine oxide to electron-deficient alkenes. Additionally, no tedious chromatographic procedures were required to isolate the tertiary phosphine oxides 1 from the reaction mixture; simple recrystallization or vacuum distillation could be used to afford analytically pure samples. Compounds 1a-e,g were isolated as white solids with sufficiently high melting points, while compound 1f was a colorless oil at ambient temperature. Their structures were confirmed by <sup>1</sup>H,  $^{13}C{^{1}H}$  and  $^{31}P$  spectroscopies, and HRMS. The structure of **1c** was studied by single crystal X-ray crystallography; the crystals suitable for this analysis were grown by slow evaporation of a Et<sub>2</sub>O solution. The ORTEP diagram is shown in Figure 1. The three P–C bonds of **1c** are nearly equal in length (1.811(1) Å); this is typical for diaryl alkyl tertiary phosphine oxides.



Figure 1. ORTEP representation of 1c showing 50% probability thermal ellipsoids

The results obtained in the current and previous studies allow some generalizations to be made. The reactivity of P(O)–H compounds in the PBu<sub>3</sub>-catalyzed addition to electron-deficient alkenes follows the trend: Ph(EtO)P(O)H < (EtO)<sub>2</sub>P(O)H << Ph<sub>2</sub>P(O)H. This indicates that replacement of alkoxy groups by phenyl groups at the phosphorus atom provides a nonlinear effect on the reaction rate. While the reactivity of dialkyl phosphites correlates well with their pK<sub>a</sub> values,<sup>14b</sup> the acidity cannot be used to predict the reactivity of alkyl *H*-phosphinates and secondary phosphine oxides, therefore, additional effects should be taken into account. For example, alkyl *H*-phosphinates and structurally related

secondary phosphine oxides have very similar  $pK_a$  values,<sup>18</sup> but exhibit very different reactivities in the PBu<sub>3</sub>-catalyzed addition.

On the basis of kinetic studies for the reactions of tertiary phosphines with electron-deficient alkenes,<sup>19</sup> we propose the catalytic cycle shown in Scheme 2, in which methyl acrylate is used as a representative example. Initial conjugate addition by the phosphine to the alkene results in formation of phosphonium enolate 4. Direct observation of this type of zwitterion by routine spectroscopic methods is very complicated due to the known tendency of these intermediates to decompose to the corresponding starting materials. For example, the calculated lifetime for the zwitterion derived from PPh3 and acrylonitrile is only 138 fs.<sup>20a</sup> When an electron-donating group is introduced to the  $\alpha$ -position, or a bulky substituent is in the  $\beta$ -position of the activated alkene, the equilibrium concentration of the phosphonium zwitterion reduces significantly, and increased concentrations of PBu<sub>3</sub> (50-100 mol%, Table 1, entries 9-12) are necessary for such reactions to proceed at reasonable rate. During its short lifetime, the generated zwitterion 4 should deprotonate diphenylphosphine oxide to furnish reactive diphenylphosphinite anion 5. Since protonation of heteroatoms is easier than with carbon, proton transfer from diphenylphosphine oxide occurs first on the carbonyl oxygen of 4 to give enol 6, which then transforms to the thermodynamically more stable keto form 6a. Secondary kinetic isotope effects observed for related reactions support this mechanistic pathway.<sup>20</sup> As expected, the more acidic but less stable trivalent tautomeric form 7 of diphenylphosphine oxide might be involved in the deprotonation step by enolate 4. Nucleophilic attack of the phosphorus atom of the anion 5 on methyl acrylate gives phosphorylated enolate 8. The generated intermediate 8 deprotonates another molecule of diphenylphosphine oxide to give product 1b and another anion 5. Then, the attack of 5 on methyl acrylate is repeated. In the presented mechanism, PBu<sub>3</sub> actually acts as an initiator, but not a typical catalyst. Once diphenylphosphinite anion 5 been generated, the addition could proceed without the participation of  $PBu_3$  until the active species 8 is formed in the reaction mixture. According to NMR spectroscopy data, phosphonium species **6a** does not accumulate in the reaction mixture in any detectable amount, since the concentration of the preceding phosphonium enolate 4 is expected to be very small, and decomposition of **6a** to the starting materials in the presence of enolate 8 also cannot be excluded (Scheme 2).



**Scheme 2.** Proposed mechanism for the PBu<sub>3</sub>-catalyzed addition of diphenylphosphine oxide to methyl acrylate and other electron-deficient alkenes

An alternative mechanism in which PBu<sub>3</sub> acts as a base to deprotonate diphenylphosphine oxide seems to be unlikely due to the low basicity of the catalyst  $(pK_a (PBu_3)=8.4)$ .<sup>21</sup>

Based on the proposed mechanism, the reactivity of a P(O)–H compound can be generally assigned to: (i) the acidity of the P(O)–H bond; (ii) the nucleophilicity of phosphorus anions of type **5**; (iii) the ease of tautomerization to trivalent form **7**. For this reason, simple structure-reactivity relationships can be found only for chemically related P(O)–H compounds from one class (for example, a series of dialkyl phosphites),<sup>14b</sup> and attempts to find similar correlations for P(O)–H compounds from different classes has proved to be unsatisfactory. The

high reactivity of diphenylphosphine oxide in comparison with dialkyl phosphites and alkyl *H*-phosphinates can be attributed to the strongest nucleophilicity of the corresponding diphenylphosphinite anion **5** resulting from the absence of electronwithdrawing alkoxy groups at the phosphorus atom as well as the facile tautomerization of diphenylphosphine oxide to reactive trivalent species **7**.<sup>22</sup>

#### Conclusion

In summary, the PBu<sub>3</sub>-catalyzed addition of diphenylphosphine oxide to unsubstituted, as well as  $\alpha$ - and  $\beta$ -substituted electron-deficient alkenes has been developed. This methodology provides efficient access to a range of tertiary phosphine oxides under neutral conditions with high atom economy. The synthetic procedure is facile<sup>23</sup> and allows catalyst recovery from the reaction mixture. Current studies are focused on further exploration of the substrate scope and mechanistic implications of the proposed methodology.

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#### Supplementary data

Detailed experimental procedures and full characterization for compounds **1a-g**, copies of <sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H}, <sup>31</sup>P{<sup>1</sup>H} NMR spectra for **1a-g**, and table with X-ray crystallographic data for **1c**. CCDC 1815742 (**1c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data\_request/cif.

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23. To a stirred mixture of diphenylphosphine oxide (5 mmol, 5 mL of MeCN) with PBu<sub>3</sub> (5-100 mol%, see Table 1), a solution of the electron-deficient alkene (5 mmol, 10 mL of MeCN) was added dropwise over 15 min; the mixture was then stoppered and stirred at room temperature for 0.5-48 h (see Table 1). After reaction completion (<sup>31</sup>P NMR spectroscopy), the solvent was removed under reduced pressure. In the case of the reaction of *trans*-methyl crotonate, the residue was distilled (oil pump) under argon to give PBu<sub>3</sub> (low-boiling fraction) and the corresponding phosphine oxide **1f** as a colorless oil (high-boiling fraction). In the case of products **1a-e,g**, the residue was washed with *n*-pentane to give a white solid, which was recrystallized from Et<sub>2</sub>O upon cooling, and then dried. PBu<sub>3</sub> can be recovered from *n*-pentane by vacuum distillation.

- 1) Tributylphosphine catalyzes addition of diphenylphosphine oxide to activated alkenes
- 2)  $\beta$ -Substituted  $\alpha$ , $\beta$ -unsaturated esters reacted well under the conditions developed
- 3) Gram-scale synthesis of tertiary phosphine oxides was performed