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Tributylphosphine catalyzed addition of diphenylphosphine oxide to unsubstituted and substituted electron-deficient alkenes

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ABSTRACT

The PBu_3-catalyzed conjugate addition of diphenylphosphine oxide to unsubstituted and substituted electron-deficient alkenes is reported. β-Substituted α,β-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 work-up 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.

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.[1] Due to their hydrolytic, thermal and oxidative stability, tertiary phosphine oxides are versatile ligands for the extraction of transuranic,[2] rare-earth[3] and noble metals;[4] as well as the stabilization of quantum dots and other metal nanoparticles.[5] Furthermore, tertiary phosphine oxides are well-established flame retardants for polymers.[6] 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.[7] 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.[8] 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, $Ca(OH)_2$, NaH, *n*-BuLi, Et_2Zn;[7,9] transition metal salts;[10] or radical initiators such as AIBN.[11] Despite the abundance of examples where tertiary phosphines are used as organocatalysts in Michael-type additions for carbon-carbon and carbon-heteroatom bond formation,[12] there exist only a few reports regarding the phosphine-catalyzed Pudovik reaction. Recently, Han and co-workers introduced PMe_3 as an efficient and easily removed catalyst for the addition of dialkyl phosphites, alkyl *H*-phosphinates and secondary phosphine oxides to electron-deficient alkenes.[13] Our group, as well as Kim and co-workers, developed an efficient PBu_3-catalyzed Pudovik reaction, that can be performed without a protective inert atmosphere and easy catalyst recovery.[14] 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_3 was varied with respect to the nature of unsaturated reagent (typically, 5–50 mol% of the catalyst were required).[14b,c]

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_3 was examined under the conditions developed previously for the reaction using dialkyl

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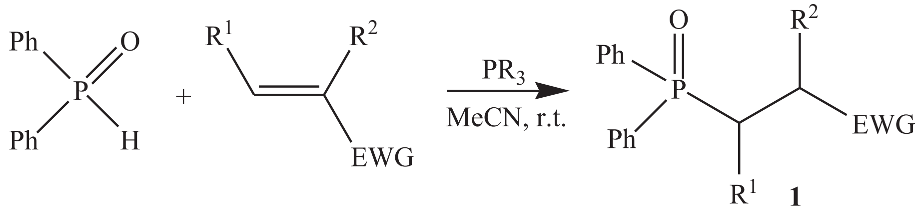
phosphites as substrates.[14b,c] α-Substituted methyl methacrylate was examined first, since due to the relatively low reactivity of this alkene in phosphine-catalyzed transformations, the synthetic outcome depends significantly on small variations of the reaction conditions. MeCN was used as a solvent, which facilitates the P(O)–H bond addition.[14,15] We were pleased to find that the application of PBu_3 (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.[14b] When lower concentrations of the catalyst were used, the yield of **1a** decreased dramatically (Table 1, entries 2, 3). With less nucleophilic PPh_3, 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_3-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 α-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.[16]

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_3 in MeCN. However, when PBu_3 was added to the equimolar mixture of diphenylphosphine oxide with methyl acrylate (or acrylonitrile) in MeCN, by-product **2** (<10%) could be detected by ^{31}P NMR spectroscopy of the crude reaction mixture. Evidently, product **2** could result from phosphine-catalyzed dimerization of the activated alkene (Rauhut-Currier reaction)[17] 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_3 is less prone to form 1:2 adducts **2** than PMe_3.[13c]

Noting that diphenylphosphine oxide possessed higher reactivity in the PBu_3-catalyzed addition to electron-deficient alkenes than the simpler dialkyl phosphites, we directed our efforts to broaden the reaction scope using β-substituted activated alkenes. All previous attempts to perform such additions in the presence of tertiary phosphines using dialkyl phosphites and alkyl *H*-phosphinates as substrates were unsuccessful even under harsh reaction conditions.[14b] The inertness of β-substituted activated alkenes in phosphine-catalyzed reactions is ubiquitous and generally explained by slow addition of tertiary phosphines to these substrates due to steric hindrance of the terminal carbon atom.[17] To our delight, the PBu_3 (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_3 (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 β-carbon atom, also reacted with diphenylphosphine oxide in the presence of PBu_3 (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_3 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 ^{31}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_3-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

Table 1
Conjugate addition of diphenylphosphine oxide to electron-deficient alkenes under phosphine catalysis.[a]



Entry	PR_3 (mol%)	R^1	R^2	EWG	Product	Time (h)	Yield **1** (%)[b]
1	PBu_3 (50)	H	Me	CO_2Me	**1a**	2	96
2	PBu_3 (30)	H	Me	CO_2Me	**1a**	4	70
3	PBu_3 (10)	H	Me	CO_2Me	**1a**	4	<5
4	PPh_3 (50)	H	Me	CO_2Me	**1a**	48	0
5	PBu_3 (5)	H	H	CO_2Me	**1b**	0.5	90
6	PBu_3 (30)	H	CH_2CO_2Me	CO_2Me	**1c**	1	95
7	PBu_3 (5)	H	H	CN	**1d**	0.5	79
8	PBu_3 (20)	H	H	$CONH_2$	**1e**	1	91
9	PBu_3 (50)	Me	H	CO_2Me	**1f**	12	77
10	PBu_3 (50)	Me	H	CO_2Me	**1f**	24	77
11	PBu_3 (100)	Me	H	CO_2Me	**1f**	8	77
12	PBu_3 (100)	Ph	H	CO_2Me	**1g**	48	68

[a] Reagents and conditions: diphenylphosphine oxide (5 mmol), alkene (5 mmol), PR_3 (5–100 mol%), MeCN (15 mL).
[b] Isolated yield.