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Alcohol-Based Michaelis-Arbuzov Reaction: an Efficient and Environmentally-Benign Way for C-P(O) Bond Formation†

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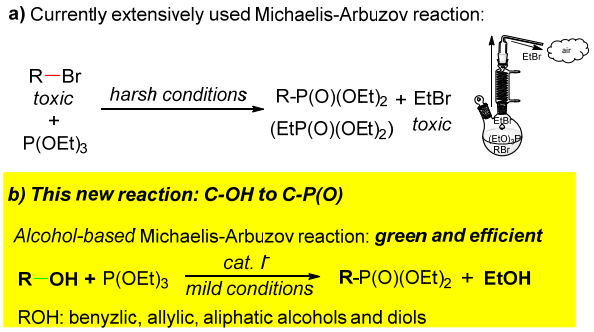
The famous Michaelis-Arbuzov reaction is extensively used both in the laboratory and industry to manufacture tons of the widely-useful organophosphoryl compounds every year. However, this method and the modified Michaelis-Arbuzov reactions developed recetnly still have some limitations. We now report a new alcohol-version of the Michaelis-Arbuzov reaction that can provide an efficient and environmentally-benign way to address the problems of the known Michaelis-Arbuzov reactions. That is, a wide range of alcohols can readily react with phosphites, phosphonites, and phosphinites to give all the three kinds of phosphoryl compounds (phosphonates, phosphinates, and phosphine oxides) by an *n*-Bu_4NI-catalyzed efficient C-P(O) bond formation reaction. This general method can also be easily scaled up and used for further synthetic transformations in one-pot.

Organophosphorus compounds containing a carbon-phosphoryl bond C-P(O) have wide and significant applications in medicinal and agricultural chemistry.[1,2] For example, fosfomycin is a clinically used antibiotics,[2a] glyphosate[2b] and glufosinate[2c] are commercially prepared herbicides. As exemplified by Horner-Wadsworth-Emmons reactions, they are also widely used in organic synthesis and catalysis.[1a-1c,3] In addition, organophosphorus compounds also have wide applications in material chemistry,[4] e.g., phosphoryl compounds-based metal extractants have been well known,[4c-4d] and the development of environment-benign fire retardants based on phosphoryl compounds is of current concern because fire retardancy is another unique feature of these compounds.[4e-4f]

Despite the importance of the organophosphoryl compounds, general and efficient methods for their preparation (the C-P(O) bond formation reactions) are limited.[5] The Michaelis-Arbuzov reaction of trialkyl phosphites with alkyl halides at high temperatures (Scheme 1a),[6] a landmark in organophosphorus chemistry developed more than one hundred years ago, is used world-widely to manufacture tons of the organophosphoryl compounds every year. However, drawbacks of this famous reaction are also obvious. In addition to the use of the toxic alkyl halides, the concomitant generation of an equivalent of low-boiling ethyl bromide is inevitable, which can cause side reactions, low atom efficiency, and environmental problems.



Scheme 1. Methods for organophosphonate synthesis.

To address these drawbacks, modified methods were later developed. For example, the groups of Mioskowski and Michalski reported Michaelis-Arbuzov rearrangements of trivalent phosphorus esters using catalytic amounts of trimethylsilyl Lewis acids instead of stoichiometric amount of alkyl halides.[7] More recently, the groups of Wiemer, Mohanakrishnan, and Iranpoor indepently reported ZnI_2, $ZnBr_2$, or PPh_3/DDQ-mediated Michaelis-Arbuzov reactions of trivalent phosphorus esters using alcohols to replace the alkyl halides.[8] However, these modified methods still have limitations. For example, the P(III) compounds used in the former method are not commercially available and require tedious preparation procedures; while the latter methods generally require anhydrous conditions and stoichiometric amount of the activators, but are still restricted to the more

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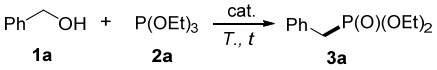
† Electronic Supplementary Information (ESI) available: Experimental details, condition screening tables, mechanistic studies, and characterization and copies of the ^1H and ^{13}C NMR spectra of the products. See DOI:10.1039/x0xx00000x

reactive allylic and benzyl alcohols. To our knowledge, no direct and efficient transformation of the aliphatic alcohols' C-O bond into C-P(O) bonds has been known so far, very possibly because the activation of aliphatic alcohols' C-O bond is more challenging than those of the more reactive alcohols.

Herein we disclose an efficient and environmentally-benign method to address the problems of the known Michaelis-Arbuzov reactions (Scheme 1b). During our studies aiming at developing new and efficient ways for the preparation of organophosphorus compounds,[5i-5j,9] we accidently found that the Michaelis-Arbuzov reaction can be performed by using alcohols rather than the toxic alkyl halides as the substrates. That is, by heating a mixture of a phosphite with the readily available, cheap, and environmentally-benign alcohol[10] in the presence of a catalytic amount of an iodide, a phosphonate can be efficiently generated in a high yield. This method is found to be a general way for C-P(O) bond formation applicable to a wide range of alcohols and P(III) compounds (phosphites, phosphonites, and phosphinites) to prepare all the three kinds of C-P(O) compounds (phosphonates, phosphinates and phosphine oxides). It is also noted that this reaction should belong to the category of transformation of the abundant C-O bonds to other chemical bonds, which is currently a quite hot topic. However, direct and efficient transformation of the C-O bond of an alcohol especially to the C-P(O) bond is limited so far.[10]

As shown in Table 1, referring to the dehydrative coupling of C-, O- and N-nucleophiles with alcohols[11] catalyzed by an alkyl bromide,[11d-11f] we initially expected that a similar coupling might occur with a dialkyl phosphite. However, the expected benzyl phosphonate (**3a**) was not detected at all after heating a mixture of benzyl alcohol (**1a**) and $HP(O)(OEt)_2$ in the presence of 10 mol% $PhCH_2Br$ (entry 1). Interestingly, however, a further study revealed that by using triethyl phosphite $P(OEt)_3$ (**2a**) instead, the target **3a** could be produced in a considerable yield (entry 2).[12-14] The yield of **3a** could be improved to 85% by co-adding 10 mol% tetrabutylammonium iodide (*n*-Bu_4NI) (entry 3). As shown by entry 4, *n*-Bu_4NI alone could efficiently catalyze the reaction to give a high yield of **3a**. Furthermore, the reaction could be efficiently carried out at a reduced temperature (125 °C, entry 5) and with a lower *n*-Bu_4NI loading (2 mol%, entry 6). Other catalysts such as *n*-Bu_4NBr and KI were also tested, but they only gave **3a** in much lower yields (entries 7-8).[14,15] The iodide catalyst was found essential for this reaction, because in the absence of *n*-Bu_4NI, only a negligible amount of **3a** was observed (entry 9).[14,16] Moreover, to obtain a higher yield of the product by distilling off the generated byproduct EtOH to drive the reaction to proceed more completely, the reaction was also investigated in an unsealed tube reactor equipped with a condenser (entry 10).[17] However, only the same yield with that of the optimal reaction performed in the sealed tube reactor (entry 6) was obtained. Hence, the reaction was still performed in sealed tube reactor for convenience's sake. ***Practically importantly, even an industrial-grade $P(OEt)_3$ (ca. 75% purity) can be directly used as the substrate without decreasing the yield of 3a at all (entry 6)!***

Table 1. Iodide-catalyzed coupling of $PhCH_2OH$ with $P(OEt)_3$ forming $PhCH_2P(O)(OEt)_2$.[a]



1a **2a** **3a**

entry	cat. (mol%)	*T.*, *t*	**3a**%[b]
1[c]	$PhCH_2Br$ (10)	150 °C, 24 h	0
2	$PhCH_2Br$ (10)	150 °C, 12 h	48 (43)
3	$PhCH_2Br$ (10) *n*-Bu_4NI (10)	150 °C, 12 h	94 (85)
4	*n*-Bu_4NI (10)	150 °C, 12 h	95 (90)
5	*n*-Bu_4NI (10)	125 °C, 24 h	95 (90)
6[d]	***n*-Bu_4NI (2)**	***125 °C***, 24 h	***97 (90)***
7	*n*-Bu_4NBr (2)	125 °C, 24 h	40
8	KI (2)	125 °C, 24 h	39
9	none	125 °C, 24 h	<1[15,16]
10[e]	*n*-Bu_4NI (2)	125 °C, 24 h	(90)

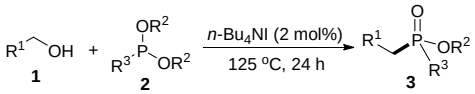
[a] Unless otherwise noted, the neat mixture of **1a** (0.50 mmol), **2a** (0.75 mmol), and a catalyst sealed under N_2 in a 20 mL Schlenk tube was heated for 24 h and then analyzed by TLC/GC-MS. [b] GC yields (isolated yields in parentheses) based on **1a**. [c] $HP(O)(OEt)_2$ was used instead of **2a**. [d] 2.0 Equiv. of an industrial-grade **2a** (ca. 75% of **2a**, others are $HP(O)(OEt)_2$, $P(O)(OEt)_3$, etc.) could also be directly used without pre-purification to give the same good result. The excess amount of **2a** could be recovered in 60~65% yields by column chromatography in small scale reactions or by vacuum distillation in large scale ones. [e] The reaction mixture added in an unsealed tube reactor (20 mL) equipped with a normal condenser was heated at 125 °C under N_2.

As shown in Table 2, this method is a rather general way for preparation of the phosphonates. With the exception of 4-nitrobenzyl alcohol that gave a complex mixture (entry 11), like the model reaction (entry 1), both electron-rich and -deficient benzylic alcohols including those bearing hydroxyl (**3b**), methoxy (**3c**-**3f**), halogen (**3g**-**3i**), and cyano (**3j**) groups, all reacted efficiently with **2a** to give good to high yields of the desired products (entries 2-10). Similarly, naphthylmethanols also afforded high yields of the corresponding phosphonates (entries 12-13). Heteroarylmethanols such as 2-thienyl- and 3-indolyl methanols could also afford excellent yields of the products (entries 14-15). Allylic alcohols such as cinnamyl alcohol and (*E*)-hex-2-en-1-ol also specifically produced the linear products in high yields without the formation of the possible branched regioisomers (entries 16-17).

Similar to $P(OEt)_3$ (**2a**), other phosphites **2b**-**2e** also reacted efficiently with alcohols to give the desired phosphonates in good yields (entries 18-23). Worth noting is that, not limited to the more reactive benzylic and allylic alcohols, the much less reactive aliphatic alcohols could also successfully afford the corresponding alkylphosphonates in satisfactory yields by replacing $P(OEt)_3$ with $P(O\textit{i}\text{-}Pr)_3$ (entries 20-21). Herein $P(O\textit{i}\text{-}Pr)_3$ was found to be a more advantageous reagent than $P(OEt)_3$, because the reaction of $P(OEt)_3$ led to the formation of byproduct diethyl ethylphosphonate and consequently difficult purification and lower yields of the desired products.[18] In addition, this P-alkylation protocol could also be extended to phosphonites. Thus, diethyl methylphosphonite (**2f**) reacted

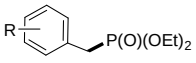
efficiently with **1a** at a reduced temperature of 100 °C to produce the corresponding phosphinate **3x** in 80% yield (entry 24).

Table 2. *n*-Bu_4NI-catalyzed synthesis of phosphonates and phosphinates via coupling of alcohols with phosphites or phosphonites.[a]

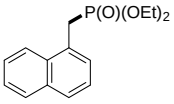


1 2 3

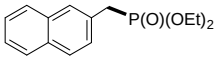
2a: R^2 = Et, R^3 = OEt; **2b:** R^2 = Me, R^3 = OMe;
2c: R^2 = *i*-Pr, R^3 = O*i*-Pr; **2d:** R^2 = *n*-Bu, R^3 = O*n*-Bu;
2e: R^2 = Ph, R^3 = OPh; **2f:** R^2 = Et, R^3 = Me



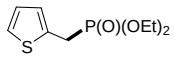
(1) R = H, **3a**: 90% (90%, 4.01g)[b]
(2) R= 4-OH, **3b**: 65%
(3) R = 2-MeO, **3c**: 85%
(4) R = 3-MeO, **3d**: 84%
(5) R = 4-MeO, **3e**: 85%
(6) R = 3,4,5-$(MeO)_3$, **3f**: 75%
(7) R = 4-F, **3g**: 81%
(8) R = 2-Cl, **3h**: 80%
(9) R = 4-Br, **3i**: 90%
(10) R= 4-CN, **3j**: 80%
(11) R = 4-NO_2, **3k**: complex



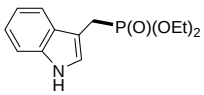
(12) **3l**: 86%



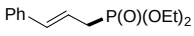
(13) **3m**: 90%



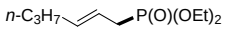
(14) **3n**: 70%[c]



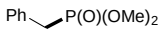
(15) **3o**: 83%[c]



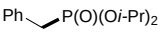
(16) **3p**: 90%



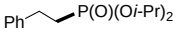
(17) **3q**: 87%



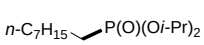
(18) **3r**: 85%



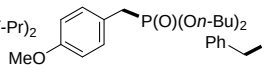
(19) **3s**: 83%



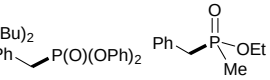
(20) **3t**: 68%[d]



(21) **3u**: 51%[d]



(22) **3v**: 85%

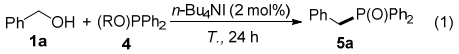


(23) **3w**: 72%[c]

(24) **3x**: 80%[e]

[a] Unless otherwise noted, see entry 6 of Table 1 for detailed conditions. Isolated yields based on **1**. [b] 20 mmol scale, 3 mol% *n*-Bu_4NI, 130 °C. [c] 5 mol% *n*-Bu_4NI. [d] 15 mol% *n*-Bu_4NI, 150 °C. [e] 100 °C.

This method was further extended to the synthesis of phosphine oxides by reacting alcohols with diphenylphosphinites **4**. However, under the above standard conditions, the reaction of **1a** and ethyl diphenylphosphinite (**4a**) only afforded a low yield of the target **5a** (eq. 1, entry 1). Fortunately, by simply reducing the reaction temperature to 85 °C, both **4a** and phenyl diphenylphosphinite (**4b**) could readily react with **1a** to give the corresponding phosphine oxide **5a** in high yields (entries 2-3, methods A and B).



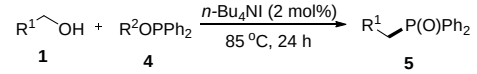
1a 4 5a (1)

4a: R = Et; **4b**: R =Ph

1) **1a/4a** = 0.50/0.75 (mmol), 125 °C, **5a**% = 25%
2) **1a/4a** = 1.0/0.50 (mmol), 85 °C, **5a**% = 86% (Method A)
3) **1a/4b** = 0.50/0.75 (mmol), 85 °C, **5a**% = 85% (Method B)

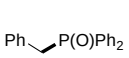
This condition was then extended to the preparation of various phosphine oxides from diphenylphosphinites **4** and alcohols. Employing method A, benzylic alcohols, heteroaryl methanols, and allylic alcohols afforded moderate to high yields of the target phosphine oxides (Table 3, entries 1-8). Method B is more suitable for less reactive aliphatic alcohols. Thus, moderate yields of the target alkyl phosphine oxides were obtained by using 10 mol% of *n*-Bu_4NI at 120 °C (entries 9-10). Worth noting is that, this protocol could also be extended to diols to obtain the corresponding bisphosphine oxides, the key precursors for bidentate phosphine ligands extensively used in metal-catalyzed reactions. Thus, various aromatic and aliphatic diols all reacted efficiently with **4b** to successfully produce the desired bisphosphine oxides (entries 11-18).

Table 3. *n*-Bu_4NI-catalyzed preparation of alkyl phosphine oxide from alcohols.[a]

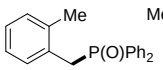


1 4 5

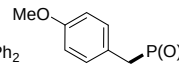
4a: R^2 = Et; **4b:** R^2 = Ph



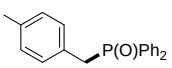
(1) **5a**: 86% (A)



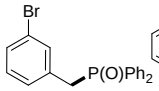
(2) **5b**: 85% (A)



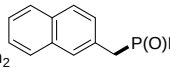
(3) **5c**: 91% (A)



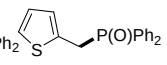
(4) **5d**: 72% (A)



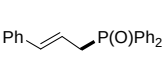
(5) **5e**: 83% (A)



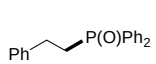
(6) **5f**: 79% (A)



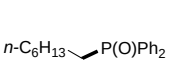
(7) **5g**: 46% (A)



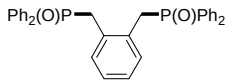
(8) **5h**: 82% (A)



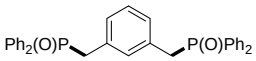
(9) **5i**: 73% (B)[b]



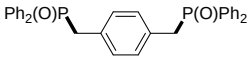
(10) **5j**: 67% (B)[b]



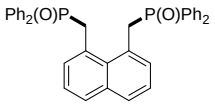
(11) **5k**: 61% (B)[c] (60%, 3.04 g)[d]



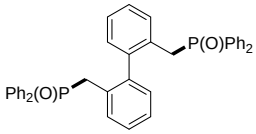
(12) **5l**: 65% (B)[c]



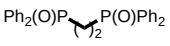
(13) **5m**: 63% (B)[c]



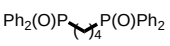
(14) **5n**: 42% (B)[c]



(15) **5o**: 38% (B)[c]



(16) **5p**: 28% (B)[b]



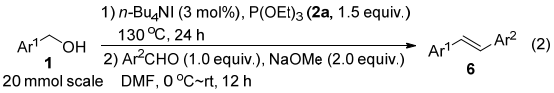
(17) **5q**: 48% (B)[b]

(18) **5r**: 46% (B)[b]

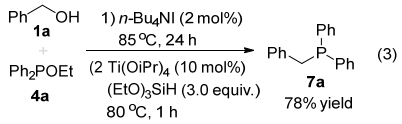
[a] Unless otherwise noted, see eq. 1 for conditions of methods A (isolated yield based on **4a**) and B (isolated yield based on **1**). [b] 10 mol% *n*-Bu_4NI, 120 °C. [c] 5 mol% *n*-Bu_4NI. [d] 10 mmol scale.

Synthetically importantly, this new method could be easily performed in relatively large scales. Thus, good yields of **3a** and **5k** could be obtained in good yields from the corresponding gram-scale reactions (entry 1, Table 1, and entry 11, Table 3). Besides, taking advantage of the high yields of phosphonates **3**, one-pot gram-scale synthesis of substituted olefins starting from alcohols **1** and aldehydes could be demonstrated. As shown in eq. 2, a 20 mmol scale reaction of **1a** and **2a** followed by treatment with PhCHO under Horner-Wadsworth-Emmons conditions[1a-1c,3] readily afforded 71% yiled (2.56 g) of stilbene **6a** (entry 1). Similarly,

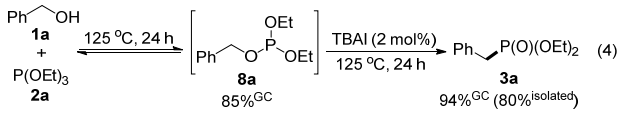
(*E*)-3,4,4',5-tetramethoxystillbene (**6b**), a potent apoptosis-inducing agent in microtubule polymerization,[19] could also be produced in one-pot in 55% overall yield (3.35 g, eq. 2, entry 2). Furthermore, one-pot synthesis of phosphine ligands is also possible (eq. 3). Thus, P-alkylation of **4a** with **1a** followed by a Ti-catalyzed reduction[20] of the in situ generated **5a** readily gave the target phosphine **7a**.[21]

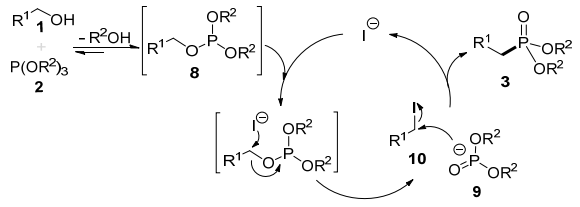


1) **6a**: $Ar^1 = Ar^2 = Ph$, 71% (2.56 g)
2) **6b**: $Ar^1 = 3,4,5\text{-}(MeO)_3C_6H_2$, $Ar^2 = 4\text{-}MeOC_6H_4$, 55% (3.35 g)
(A potent apoptosis-inducing agent in microtubule polymerization[15])



As to the mechanism of this new reaction, it was confirmed that transesterification of **1a** with **2a** could occur to give phosphite **8a** in 85% GC yield in the absence of the catalyst (eq. 4).[13,14,22,23] By adding *n*-Bu_4NI, **8a** then isomerized to give **3a**.[14,23] Therefore, it can be assumed that the transesterification reaction between **1** and **2** giving **8** is the initial step of the reaction.[14,24] Next, attack of the iodide on the alkylenyl carbon of **8** may occur and lead to C-O cleavage and generation of phosphoryl anion **9** and alkyl iodide **10** (Scheme 2). Herein the generation of **10** could be supposed by the observation of the formation of ethers $(PhCH_2)_2O$ and $PhCH_2OEt$ (via the reaction of **1a** and byproduct EtOH with in situ generated $PhCH_2Br$[11d]) in the reaction of **1a** and *n*-Bu_4NBr with quantitative **2a**.[14,25] Finally, **9** and **10** may couple to afford products **3**[14,26] and regenerate the iodide catalyst.





Scheme 2. Proposed mechanism.

Regarding the rate-determining step of the whole reaction, the initial transesterification reaction that can even occur at room temperature[14,24] is clearly not the rate-determining step. Likewise, the last reaction of phosphoryl anion **9** and alkyl halides **10** giving the products is also not the rate-determining step, because we ourselves have found that **5a** could be readily obtained from a similar reaction of $PhCH_2Br$ and an *in situ* generated phosphoryl anion[26] and literature reports also revealed that the reaction can readily proceed at room temperature even with the more bulky secondary alkyl halides.[27] In contrast, the second nucleophilic attack of iodide at the alkylenyl carbon of **8** followed by a C-O bond cleavage to generate **9** and **10** is most likely the rate-determining step of the whole reaction. This is consistent with the observations of the reactions. For example, conversion of **8** to **3** requires both the catalyst and a higher reaction temperature (eq. 4).[14] Besides, both steric properties of **1** and **2** can influence the reaction greatly as the reactions of $P(Oi\text{-}Pr)_3$ gave no byproducts (Table 2, entries 20-21)[18] and, most likely for the same reason, the sterically more bulky secondary alcohols can not be used in the present method currently.

Conclusions

In summary, we accidentally discovered an *n*-Bu_4NI-catalyzed efficient C-P(O) bond formation reaction of alcohols and triorganyl phosphites. A variety of alcohols, including the more reactive benzyl and allylic alcohols, the less reactive aliphatic alcohols, and even diols, can be readily used to react with phosphites, phosphonites, and phosphinites, providing a general way for preparation of all three kinds of phosphoryl compounds (phosphonates, phosphinates, and phosphine oxides). This method can also be easily scaled up and used for further synthetic transformations in one-pot, such as in the Horner-Wadsworth-Emmons reaction and for the synthesis of a phosphine ligand. Since the conventional Michaelis-Arbuzov reaction and the modified methods developed recently still have some limitations, this general new method can be regarded as a green alcohol-version of the Michaelis-Arbuzov reaction as it provides an efficient and environmentally-benign way to prepare the widely-useful P(O) compounds.

Acknowledgements

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12 Phosphite $P(OEt)_2(OCH_2Ph)$ formed via transesterification was also observed in 28% GC yield with trace double transesterified $P(OEt)(OCH_2Ph)_2$ (ref. 13). Traces of $EtP(O)(OEt)_2$ and $PhCH_2P(O)(OEt)(OCH_2Ph)$ derived from the isomerization of **2a** and $P(OEt)(OCH_2Ph)_2$ were also observed.

13 Transesterification of phosphorus compounds with alcohols: *(a)* F. W. Hoffmann, R. J. Ess and R. P. Usingef, Jr., *J. Am. Chem. Soc.*, 1956, **78**, 5817; *(b)* F. W. Hoffmann, R. G. Roth and T. C. Simmons, *J. Am. Chem. Soc.,* 1958, **80**, 5937.

14 See the †ESI for details.

15 The reaction was also investigated under other conditions (at lower temperatures, in solvents, using more or less loadings of **2a**), but no better results were obtained.

16 $P(OEt)_2(OCH_2Ph)$ (ref. 13) was observed as the major product in 85% GC yield (see also eq. 4).

17 We appreciate one of the reviewers for this kind suggestion. However, possibly due to the ready transesterification reaction of **1** and **2** that can even occur at room temperature (see ref. 24 and †ESI), as we observed, there is no need to distill out byproduct EtOH from the reaction vessel using an unsealed reactor.

18 Most possibly due to the close steric hindrance and close reactivities of the Et and aliphatic alkyl groups, nucleophilic attack of I^- at the CH_2 of Et and aliphatic alkyl groups (according to the proposed mechanism) both occurred to give a mixture of the desired product and byproduct diethyl ethylphosphonate in the reactions of $P(OEt)_3$. In contrast, the use of $P(O\textit{i}\text{-Pr})_3$ could successfully suppress the same side reaction of $P(O\textit{i}\text{-Pr})_3$ (the nucleophilic attack of I^- at the CH of *i*-Pr) and generation of the byproduct, most likely due to the greater steric hindrance and much lower reactivity of the more bulky *i*-Pr than the aliphatic alkyl groups.

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21 Due to its sensitive nature toward air, generation of **7a** was confirmed by transformation into phosphonium salt $[PPh_2(CH_2Ph)_2]Br$.

22 Since the reaction of **1** and **2** is a reversible equilibrium (ref. 13), GC yield of **8a** is not quantitative. Addition of *n*-Bu_4NI could then drive the reaction to complete and effectively gave **3a** in a high yield.

23 Similarly, the blank reaction of **1c** and **4a** also afforded mainly transesterified $Ph_2POCH_2C_6H_4OMe$ (ref. 13) as isolated and confirmed by NMR analysis. $Ph_2POCH_2C_6H_4OMe$ was then transformed into **5c** catalyzed by *n*-Bu_4NI. See the †ESI for details.

24 This is also supported by a room temperature reaction of **1a** and **2a** that gave **8a** as the sole product.

25 The reaction of **1a** and *n*-Bu_4NBr in the presence of quantitative **2a** readily afforded considerable yields of ethers $(PhCH_2)_2O$ and $PhCH_2OEt$ (right), which should be produced by the reaction of **1a** and byproduct EtOH with the in situ generated $PhCH_2Br$ (ref. 11d). In contrast, no reaction occurred at all in the blank reaction of **1a** and *n*-Bu_4NBr without **2a** (left), revealing that $PhCH_2Br$ can not be generated from a blank reaction of **1a** and *n*-Bu_4NBr. Thus, the only way to generate $PhCH_2Br$ is via the proposed mechanism in the presence of **2a** (Scheme 2).

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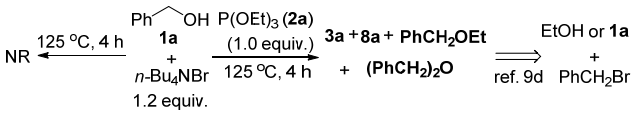

26 The coupling of $PhCH_2Br$ and an *in situ* generated phosphoryl anion readily afforded the target product **5a**.

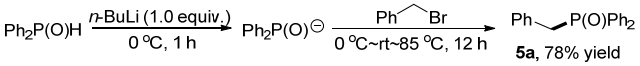

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Table of Contents

Alcohol-Based Michaelis-Arbuzov Reaction: an Efficient and Environmentally-Benign Way for C-P(O) Bond Formation

Xiantao Ma, Qing Xu,* Huan Li, Chenliang Su, Lei Yu, Xu Zhang, Hongen Cao, and Li-Biao Han*