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Lewis-acid-catalyzed phosphorylation of alcohols†

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An efficient method has been developed for reacting dialkyl H-phosphonates or diarylphosphine oxides with alcohols for constructing C–P bonds. This reaction was catalyzed by Lewis acid and involved nucleophilic substitution. A series of diphenylphosphonates and diphenylphosphine oxides were obtained, from the phosphorylation of alcohols, with good-to-excellent yields.

Introduction

Organophosphonate compounds and their derivatives play an important role in agrochemistry,[1] medicinal chemistry[2] and organic chemistry.[3] For example, calcium antagonist containing a diethyl phosphonate skeleton is a new calcium antagonist of the Fostedil series introduced in 1982.[4] Substituted phenyl- and benzylphosphonic acids have been shown to be inhibitors of human prostatic acid phosphatase.[5] In addition, they are used as general components for the preparation of functional materials, such as chemiluminescent materials,[6] fluorescent materials,[7] flame retardants[8] and OLED transmitters[9] (Fig. 1). Diaryl phosphonates are very important, but only a few methods for their synthesis have been reported. Using the classical Michaelis–Arbuzov or Michaelis–Becker reaction, dialkyl phosphonate has been synthesized from a nucleophilic phosphite and an electrophilic alkyl halide under basic conditions, but the reaction showed the disadvantages of limited availability of the starting materials and high reaction temperature.[10] To overcome these limitations, the Mohanakrishnan group developed a Lewis-acid-mediated Michaelis–Arbuzov reaction to synthesize arylmethylphosphonate and heterarylmethylphosphonate from heteroarylmethylhalides/alcohols and triethyl phosphite at room temperature[11] (Scheme 1a). The Chakravarty group developed a method for carrying out a Friedel–Crafts-type arylation of α-hydroxy phosphonates with arenes in the presence of stoichiometric amounts of $FeCl_3$ to synthesize dialkyl(di-arylmethyl)phosphonates[12] (Scheme 1b). The Walsh group reported a palladium-catalyzed α-arylation of benzylic phosphonates to diisopropyl phosphonate using aryl bromide and diaryl methyl phosphonate as raw materials, but this protocol was restricted to diisopropyl phosphonate derivatives[13] (Scheme 1c). Recently, a novel Brønsted-acid-catalyzed phosphorylation of *o*-hydroxybenzyl alcohol has been developed—leading to the synthesis of diphenylphosphonates from trialkylphosphites serving as starting materials and achieved using the phosphate-Michael addition reaction[14] (Scheme 1d). In addition, synthetic chemists have made remarkable progress in investigating methods for forming P–O bonds between P sources and alcohols in recent years, with examples of these methods including, the nucleophilic substitution reaction,[15] Atherton–Todd reaction,[16] cross-dehydrogenative coupling reaction[17] and electrophile reaction.[18] Our group focuses on the phosphorylation of ketones or aldehydes *via* the phospha-aldol-elimination (PAE) reaction catalyzed by Lewis acid or Brønsted acid.[19] In this study, an effective and green nucleophilic substitution reaction for synthesizing diphenylphosphonates was studied by constructing C–P bonds with alcohol and dialkyl phosphate as raw materials under the catalysis of Tf_2O and Lewis acid $Al(OTf)_3$ (Scheme 1e).

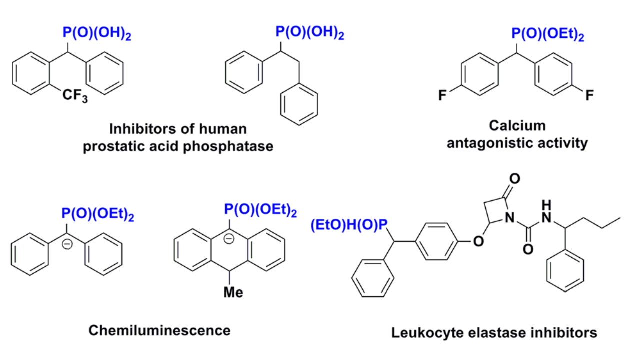

Fig. 1 Examples of functional disubstituted phosphonates and their derivatives.

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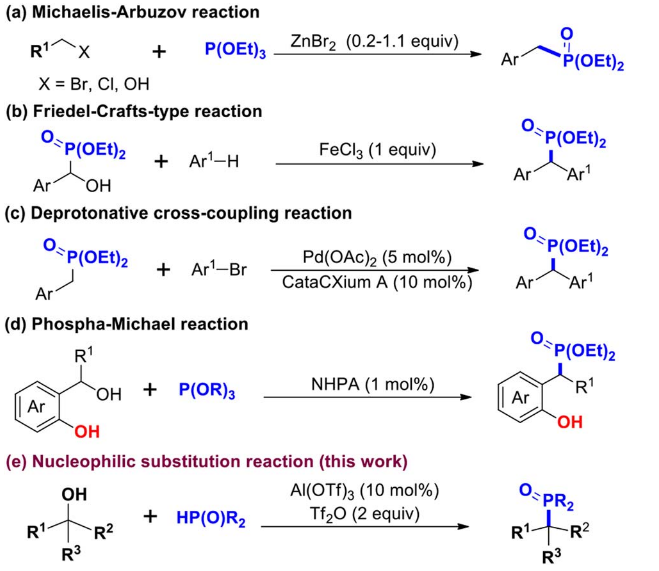
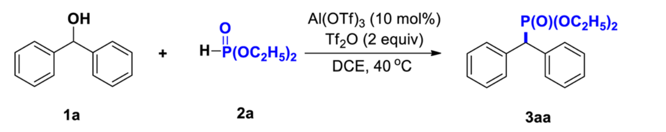


Scheme 1 Synthetic approaches to phosphorus-substituted diarylmethanes.

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



Entry	Deviation	Yield (%)
1	None	94%
2	TfOH, TsOH, H_2SO_4, AcOH instead of Tf_2O	Trace
3	$Cu(OTf)_2$ instead of $Al(OTf)_3$	15%
4	$Fe(OTf)_2$ instead of $Al(OTf)_3$	17%
5	AgOTf instead of $Al(OTf)_3$	76%
6	$AlCl_3$ instead of $Al(OTf)_3$	50%
7	$ZnBr_2$ instead of $Al(OTf)_3$	28%
8	$CuBr_2$ instead of $Al(OTf)_3$	30%
9	$FeCl_3$ instead of $Al(OTf)_3$	36%
10	CH_3NO_2, CH_3CN, THF instead of DCE	Trace
11	$PhCH_3$ instead of DCE	32%
12	Dioxane instead of DCE	16%
13	25 °C	64%
14	60 °C	25%
15	80 °C	21%
16	100 °C	19%
17	5 mol% $Al(OTf)_3$	78%
18	1.5 equiv. Tf_2O	84%
19	Without Tf_2O	8%
20	Without $Al(OTf)_3$	37%

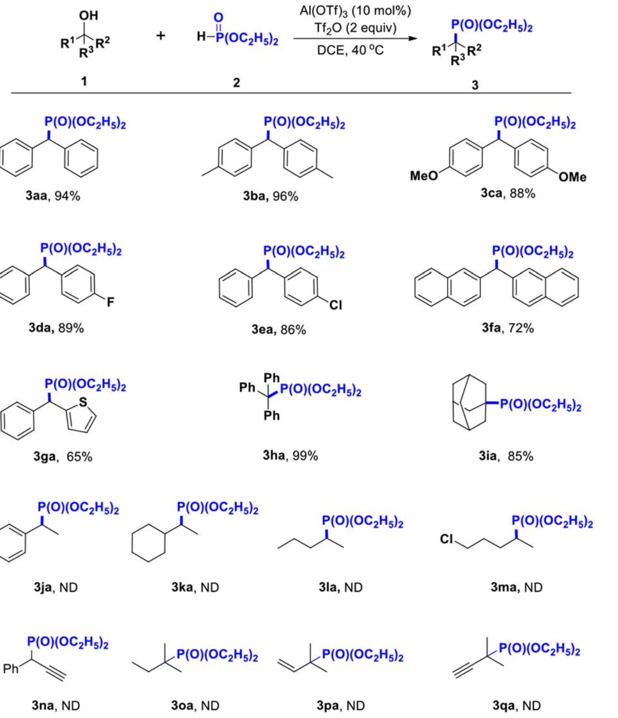
[a] Reaction conditions: diphenylmethanol (0.2 mmol), $Al(OTf)_3$ (10 mol%), diethyl phosphite (2.5 equiv.), and trifluoromethanesulfonic anhydride (2 equiv.) in dichloroethane (2 mL) at 40 °C for 14 h under air. [b] Isolated yield.

Results and discussion

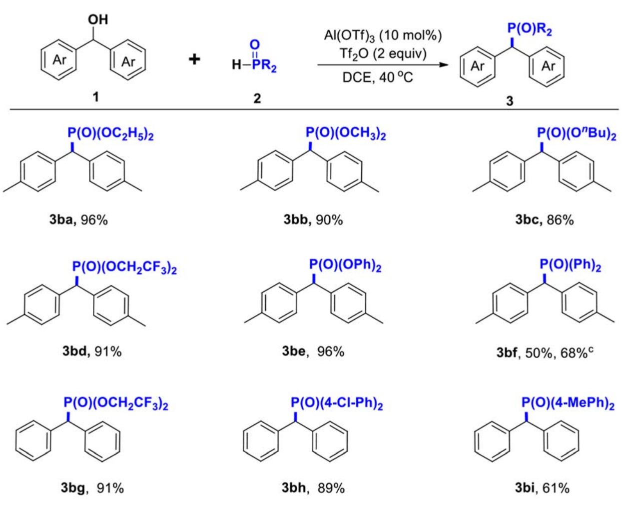
After screening a series of conditions, diethyl benzhydrylphosphonate **3aa** with 94% yield was obtained using diphenylmethanol **1a** and diethyl phosphonate **2a** as the substrates, $Al(OTf)_3$ as a catalyst and trifluoromethanesulfonic anhydride (Tf_2O) as an additive in dichloroethane (DCE) at 40 °C under air for 14 h (Table 1). Based on our previous work showing that acid as an additive plays a key role in this reaction, we were pleased to find that the yield of **3aa** was significantly better when using Tf_2O as an additive than when using other additives, such as TfOH, TsOH, H_2SO_4, and AcOH (Table 1, entry 2). Further, some Lewis acids were examined. When using $Al(OTf)_3$ as the Lewis acid, the yield of expected product was 94% (Table 1, entry 1), but when using $Cu(OTf)_2$, $Fe(OTf)_2$, AgOTf, $AlCl_3$, $ZnBr_2$, $CuBr_2$, or $FeCl_3$ instead, the expected product was afforded in lower yields (Table 1, entries 3–9). Other solvents, namely CH_3NO_2, CH_3CN, and THF, were each tested, but found to be ineffective (Table 1, entries 10–12). Finally, lower yields were observed when testing reaction temperatures and amounts of catalyst differing from those of the above optimal conditions and when carrying out certain control experiments (Table 1, entries 13–20).

Under optimized reaction conditions, various dibenzyl alcohol and diethyl phosphite substrates were investigated, as shown in Scheme 2. Electron-donating and electron-withdrawing groups on dibenzyl alcohol afforded phosphorylation products with excellent yields (**3aa–3ea**). Moreover, a moderate yield of phosphorylated product **3fa** was obtained with di-naphthalen-2-yl methanol in this catalytic system. In addition, other heteroaromatic alcohols, such as phenyl(thiophen-2-yl)methanol **1g**, produced the desired product in moderate yields. To further verify our catalytic system, tertiary alcohols bearing aryl (**1h**) and alkyl (**1i**) groups were introduced into the reaction, and excellent yields were obtained. However, when other alcohols, such as 1-phenylethanol **1j**, 1-cyclohexylethanol **1k**, pentan-2-ol **1l**, 5-chloropentan-2-ol **1m**, 1-phenyl-2-propyn-1-ol **1n**, 3-methylbutan-3-ol **1o**, 2-methyl-3-buten-2-ol **1p**, and 2-methyl-3-butyn-ol **1q** were introduced into the reaction system in respective experiments, no target product in any of these cases was obtained, which may have been the result of the instability of the alkyl carbocation formed.

Under optimized reaction conditions, the P-source substrate scope was evaluated, as shown in Scheme 3. For example, H-phosphonate and H-phosphonate oxides were introduced into respective samples to evaluate the catalytic reaction system. To our delight, the reaction with H-phosphinate proceeded to give **3ba–3bd** and **3bg** in 86–96% isolated yields. Moreover, the reaction with diphenyl phosphate proceeded, and **3be** was obtained with 96% yield. It is noteworthy that diphenylphosphine oxide **3bf** was afforded in 50% yield under optimized reaction conditions, and when extending the reaction time, the yield was increased to 68%, but when increasing the reaction temperature using a shorter reaction time did not show the best results. However, when electron-withdrawing and electron-donating groups were introduced onto diphenylphosphine oxide, the results showed that the electron-withdrawing groups were better than the electron-donating groups, attributed to the



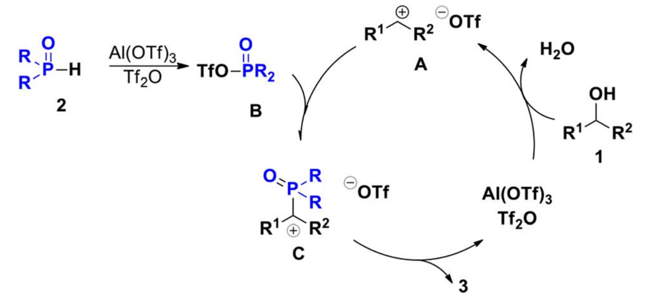
Scheme 2 Alcohol substrate scope. [a] Reaction conditions: diphenylmethanol (0.2 mmol), $Al(OTf)_3$ (10 mol%), diethyl phosphite (2.5 equiv.), and trifluoromethanesulfonic anhydride (2 equiv.) in dichloroethane (2 mL) at 40 °C for 14 h under air. [b] Isolated yield.



Scheme 3 P-source substrate scope. [a] Reaction conditions: diphenylmethanol (0.2 mmol), $Al(OTf)_3$ (10 mol%), diethyl phosphite (2.5 equiv.), and trifluoromethanesulfonic anhydride (2 equiv.) in dichloroethane (2 mL) at 40 °C for 14 h under air. [b] Isolated yield. [c] 24 h.

electronic properties, for example, for bis(4-chlorophenyl) phosphine oxide **3bh** and di-*p*-tolylphosphine oxide **3bi**, the products were obtained in 89% and 61% yields, respectively.

Based on previous reports,[8,19a,20] we proposed a plausible reaction mechanism. According to this proposal, in the presence of Lewis acid and Brønsted acid, diaryl methanol forms



Scheme 4 Proposed mechanism.

diarylmethyl cations, while the more nucleophilic intermediate **B** is obtained under the Tf_2O and $Al(OTf)_3$ system. Intermediate **B** then reacts immediately with diarylmethyl cations to obtain the target product **3** while releasing the catalyst HOTf (Scheme 4).

Conclusions

In summary, we developed an efficient green method for the synthesis of diphenylphosphonates and diphenylphosphine oxide compounds with good-to-moderate yields—to construct a C–P bond by Lewis-acid-catalyzed nucleophilic substitution reaction between dialkyl H-phosphonates or diarylphosphine oxides and diarylmethanols or trisubstituted methanol.

Data availability

All relevant experimental data are provided in the ESI.†

Author contributions

XHW, YBW and QS directed the project. The experiments were conducted and characterized by XHW, XL and YWX. XHW prepared and revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

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