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Water Determines the Products: an Unexpected Brønsted Acid-Catalyzed PO-R Cleavage of P(III) Esters Selectively Producing P(O)-H and P(O)-R Compounds[†]

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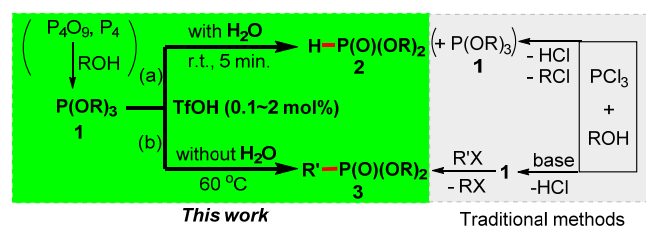
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Water is found able to determine the selectivity of Brønsted acid-catalyzed C-O cleavage reactions of trialkyl phosphites: with water, the reaction quickly takes place at room temperature to afford quantitative yields of H-phosphonates; without water, the reaction selectively affords alkylphosphonates in high yields, providing a novel halide-free alternative to the famous Michaelis-Arbuzov reaction. This method is general as it can be readily extended to phosphonites and phosphinites and a large scale reaction with much lower loading of the catalyst, enabling a simple, efficient, and practical preparation of the corresponding organophosphorus compounds. Experimental findings in control reactions and substrate extension as well as preliminary theoretical calculation of the possible transition states all suggest that the monomolecular mechanism is preferred.

Having wide applications in organic synthesis, catalysis, agricultural and medicinal chemistry, and functional materials, organophosphorus compounds are highly useful.¹ Despite their importance, general and efficient methods for their synthesis are still limited,² as heavy pollution associated with the industrial preparation of the organophosphorus compounds are notorious. Therefore, developing practically useful, clean, and efficient methods for the preparation of organophosphorus compounds possesses great scientific and industrial importance.

Hydrogen phosphonates H-P(O)(OR)₂ (**2**) and substituted phosphonates R-P(O)(OR)₂ (**3**) are two industrially important chemicals. Currently, they are prepared from the reactions of PCl₃ and ROH, which inevitably produces large amounts of wastes. As shown in Scheme 1 (right), with the concomitant

formation of HCl and RCl, PCl₃ reacts with ROH to produce **2**.³ As to the preparation of **3**, the reaction of PCl₃ with ROH is conducted in the presence of a base to generate phosphites (**1**) first, which then reacts, usually under rather harsh conditions, with a halide R'X to generate **3** (the Michaelis–Arbuzov rearrangement).^{4–7} Since side products of structurally similar phosphorous compounds were also generated (for example, **1** can be generated in the preparation of **2**), tedious purification procedures are usually required.



Scheme 1. Preparation of phosphonates **2** and **3**.

Since phosphites (**1**) can affect the catalytic activities of the transition metal catalysts used in our ongoing catalytic preparation of organophosphorus compounds starting from **2**,^{2i-1,8,9} we need a fast and simple way to remove **1** contaminated in **2**. Herein we disclose that, a Brønsted acid (perfluorinated sulfonic acids such as TfOH) can rapidly and selectively catalyze the conversion of phosphites (**1**) to H-phosphonates (**2**) via an efficient catalytic hydrolysis with water, producing highly pure H-phosphonates (**2**) (Scheme 1, left, path a). Very surprisingly, *in the absence of water*, the same Brønsted acid can efficiently catalyze the transformation of phosphites (**1**) to alkylphosphonates (**3**) under mild conditions (Scheme 1, left, path b), revealing an unprecedented mild but efficient Michaelis–Arbuzov rearrangement reaction.^{4–7} This new method may demonstrate a simple, efficient, and practical halide-free process for the preparation of **2** and **3** because phosphites (**1**) may alternatively be prepared from P₄O₆ or even elemental phosphorus (P₄) and alcohols.¹⁰

During the investigation on the reactions of P(III) esters,^{8f} we observed that direct addition of a Brønsted acid to the commercial triisopropyl phosphite (**1a**) could lead to the

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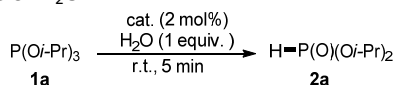
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generation of H-phosphonate $\text{HP(O)(O}i\text{-Pr)}_2$ (**2a**) in variant yields. As shown in Table 1, 26% **2a** was obtained from a neat mixture of **1a** and water in the presence of only 2 mol% $\text{Ph}_2\text{P(O)OH}$ (entry 1). This result aroused our interest, since **2a** could not be observed at all without the acid (entry 2), showing clearly **2a** is generated via a C-O cleavage of **1a** catalyzed by the acid.¹¹ Then, a variety of Brønsted acids were evaluated (entries 3-4), among which the perfluorinated sulfonic acids such as $\text{CF}_3\text{CO}_2\text{H}$, TfOH, $n\text{-C}_4\text{F}_9\text{SO}_3\text{H}$, and $n\text{-C}_8\text{F}_{17}\text{SO}_3\text{H}$ ensured rapid and complete hydrolysis of **1a** at room temperature to afford quantitative yields of **2a** by 5 min (entry 3).¹¹ However, the catalytic activity is low with other Brønsted acids such as AcOH, PhCO_2H , and PhSO_3H (entry 4).

Table 1. Brønsted acid-catalyzed C-O cleavage of $\text{P(O}i\text{-Pr)}_3$ in the presence of H_2O .^a



entry	cat. (2 mol%)	2a % ^b
1	$\text{Ph}_2\text{P(O)OH}$	26
2	none	none
3	$\text{CF}_3\text{CO}_2\text{H}$, TfOH, $n\text{-C}_4\text{F}_9\text{SO}_3\text{H}$, $n\text{-C}_8\text{F}_{17}\text{SO}_3\text{H}$	>99 (94)
4	AcOH, PhCO_2H , PhSO_3H	7~10

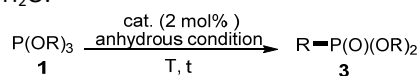
^a Reaction conditions: without using any solvent, **1a** (2.3 mmol), H_2O (1 equiv.), and catalyst (2 mol%) were mixed under air in an NMR tube at room temperature (ca. 25 °C). The tube was sealed, shaken slightly, and subjected to NMR measurement in 5 min. ^b Yields based on ^{31}P NMR analysis (isolated yields were shown in parenthesis).

Very surprisingly, in sharp contrast to above results, *in the absence of water*, the C-O bond cleavage also occur with P(OR)_3 but selectively led to Michaelis–Arbuzov rearrangement products **3** (Table 2). As mentioned above, compounds **3** have long been prepared by the legendary Michaelis–Arbuzov reaction.⁵ However, this reaction was usually conducted under very harsh conditions accompanied with a lot of side products. Recently, to improve the old Michaelis–Arbuzov method,⁵ great efforts have been devoted to develop alternative ways that can efficiently and selectively afford the products under mild conditions.⁶⁻⁷ To the best of our knowledge, the present Brønsted acid-catalyzed mild Michaelis–Arbuzov rearrangement of P(OR)_3 is unprecedented yet. Beyond this, it is also conceptually new because it was hard to imagine that such easily hydrolyzed P-O-C bonds could selectively convert to P(O)-C bond by a *protonic acid*, and this may explain why all other studies had used moisture sensitive Lewis acids.⁶⁻⁷ By comparison, the present Brønsted acid-catalyzed Michaelis–Arbuzov reaction greatly surpasses those known methods because of its simplicity, high efficiency, and high practicality.

Thus, when P(OEt)_3 (**1b**) was treated with perfluorinated sulfonic acids under the same solvent-free condition, high yields of rearranged EtP(O)(OEt)_2 (**3b**) were obtained at 60 °C (Table 2, entries 1-3). No reaction occurred without the acid (entry 4) or with other acids that were active for the catalytic hydrolysis reaction (entry 5), showing exceptional behaviour of the perfluorinated sulfonic acids in the rearrangement

reaction. The sterically less bulky P(OMe)_3 could give the corresponding phosphonate MeP(O)(OMe)_2 (**3c**) even at room temperature (entry 6).

Table 2. Brønsted acid-catalyzed C-O cleavage of P(OR)_3 in the absence of H_2O .^a



entry	1 : P(OR)_3	cat. (2 mol%)	T, t	3 : yield (%) ^b
1	1b : P(OEt)_3	TfOH	60 °C, 16 h	3b : 98 (95)
2	1b	$n\text{-C}_4\text{F}_9\text{SO}_3\text{H}$	60 °C, 16 h	3b : 96
3	1b	$n\text{-C}_8\text{F}_{17}\text{SO}_3\text{H}$	60 °C, 16 h	3b : 93
4	1b	none	60 °C, 16 h	3b : none
5	1b	other acids ^c	60 °C, 16 h	3b : none
6 ^d	1c : P(OMe)_3	TfOH	r.t., 6 h	3c : 96 (95)

^a Reaction conditions: without using any solvent, P(OEt)_3 (**1b**, 2.3 mmol) and catalyst (2 mol%) were heated under N_2 in a glass tube (10 mL). ^b GC yields using decane as the internal standard (isolated yields were shown in parenthesis). ^c AcOH, $\text{CF}_3\text{CO}_2\text{H}$, PhCO_2H , $\text{Ph}_2\text{P(O)OH}$, and PhSO_3H were tested. ^d 3.4 mmol P(OMe)_3 (**1c**) was used instead of **1b**.

The simplest TfOH was then chosen as the catalyst for substrate extension (Table 3). For reactions in the presence of water (Table 3, 3rd column), similar to **1a** (entry 1), other trialkyl, triallyl, and tribenzyl phosphites **1b-f** also afforded the corresponding H-phosphonates in quantitative yields under the solvent-free condition (entries 2-6). In the case of dimethyl phenyl phosphite **1g** (entry 7), C-O cleavage could occur at both the MeO and PhO moieties, leading to a mixture of **2c** and **2g**. Although this means the method is less suitable for unsymmetrical phosphites (entries 7-8, 17-18), the observed unexpected C-O cleavage of the PhO group inspired us to investigate the reaction of triary phosphites such as P(OPh)_3 . Pleasingly, the otherwise difficult-to-prepare HP(O)(OPh)_2 (**2i**) could easily be obtained quantitatively from the readily available P(OPh)_3 under the standard conditions (entry 9).

Worthy of mentioning is that, HP(O)(OR)_2 are currently mostly prepared by reacting PCl_3 with alcohols.³ However, since P(OR)_3 formation is inevitable and difficult to remove, HP(O)(OR)_2 are generally contaminated with a small amount of P(OR)_3 . Therefore, the present reaction provides a total solution to this long-unsolved problem. For example, as shown in eq. 1, after treated with 2 mol% TfOH, the 5 mol% contaminant P(OMe)_3 (**1c**) in HP(O)(OMe)_2 (**2c**) could be completely converted into **2c**, providing a practical method for preparation of highly pure HP(O)(OR)_2 (**2**) by simple filtration.^{12,13} This result shows that the present method is a simple, efficient, and practical way in manufacturing highly pure H-phosphonates, a class of starting material widely used for the synthesis of a range of biologically- and pharmaceutically-active functionalized organophosphorus compounds.^{2i-1,9}

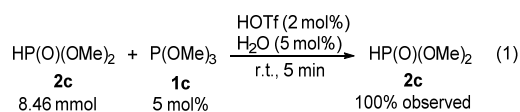
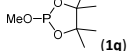
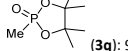
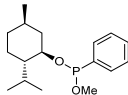
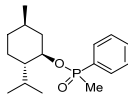


Table 3. Substrate extension for TfOH-catalyzed C-O cleavage reactions of (RO)PZ₂.^a

$$\text{H-P(O)}_2\text{Z}_2 \xleftarrow[\text{r.t., 30 min}]{\text{TfOH (2 mol\%), H}_2\text{O (1 equiv.)}} \text{(RO)PZ}_2 \xrightarrow[\text{60 }^\circ\text{C, 16 h}]{\text{TfOH (2 mol\%), anhydrous condition}} \text{R-P(O)}_2\text{Z}_2$$

entry	(RO)PZ ₂ (1)	HP(O)Z ₂ (2) ^b	RP(O)Z ₂ (3) ^c
1	P(Oi-Pr) ₃ (1a)	HP(O)(Oi-Pr) ₂ (2a): >99 (94)	<i>i</i> -PrP(O)(Oi-Pr) ₂ (3a): 15 ^d
2	P(OEt) ₃ (1b)	HP(O)(OEt) ₂ (2b): >99 (93)	EtP(O)(OEt) ₂ (3b): 96
3	P(OMe) ₃ (1c)	HP(O)(OMe) ₂ (2c): >99 (92)	MeP(O)(OMe) ₂ (3c): 95
4	P(On-Bu) ₃ (1d)	HP(O)(On-Bu) ₂ (2d): >99 (92)	<i>n</i> -BuP(O)(On-Bu) ₂ (3d): 85
5	P(Oallyl) ₃ (1e)	HP(O)(Oallyl) ₂ (2e): >99 (91)	allylP(O)(Oallyl) ₂ (3e): 94
6	P(OCH ₂ Ph) ₃ (1f)	HP(O)(OCH ₂ Ph) ₂ (2f): >99 (88)	PhCH ₂ P(O)(OCH ₂ Ph) ₂ (3f): 76
7	(MeO) ₂ P(OPh) (1g)	HP(O)(OMe) ₂ (2g): 70 (50)	MeP(O)(OMe)(OPh) (3g): 83
8	(MeO)P(OPh) ₂ (1h)	--	MeP(O)(OPh) ₂ (3h): 82
9	P(OPh) ₃ (1i)	HP(O)(OPh) ₂ (2i): >99 (91)	--
10	(MeO) ₂ PPh (1j)	HP(O)(OMe)Ph (2j): >99 (92)	MeP(O)(OMe)Ph (3j): 95
11	(MeO)PPh ₂ (1k)	HP(O)Ph ₂ (2k): >99 (90)	MeP(O)Ph ₂ (3k): 93
12	(EtO)PPh ₂ (1l)	HP(O)Ph ₂ (2l): >99	EtP(O)Ph ₂ (3l): 80 ^e
13	(<i>i</i> -PrO)PPh ₂ (1m)	HP(O)Ph ₂ (2k): >99	<i>i</i> -PrP(O)Ph ₂ (3m): <10 ^d
14	(PhCH ₂ O)PPh ₂ (1n)	HP(O)Ph ₂ (2k): >99	PhCH ₂ P(O)Ph ₂ (3n): 92
15	PhCH(CH ₃)OPPh ₂ (1o)	HP(O)Ph ₂ (2k): >99	PhCH(CH ₃)P(O)Ph ₂ (3o): 36 ^d
16	(MeO)PCy ₂ (1p)	HP(O)Cy ₂ (2p): >99 (91)	MeP(O)Cy ₂ (3p): 92 ^f
17	 (1q)	--	 (3q): 92
18	 (1r)	--	 (3r): 65

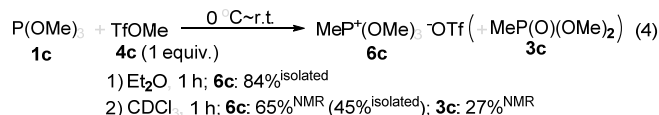
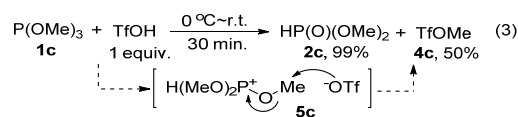
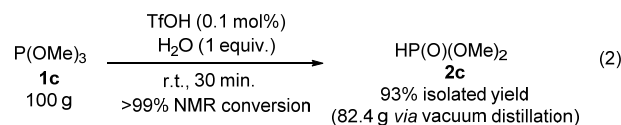
^a Reaction conditions: See Tables 1 and 2 for detailed conditions, respectively. ^b Yields based on ³¹P NMR (isolated yields were shown in parenthesis). ^c Isolated yields. ^d Complex reaction occurred with generation of byproducts. ^e 100 °C. ^f 0.56 mmol (MeO)PCy₂ in 0.5 mL toluene was heated at 100 °C.

This method could also be readily extended to phosphonites and phosphinites to prepare the corresponding H-phosphinates and H-phosphine oxides (Table 3, 3rd column, entries 10-16). Thus, H-phosphinate **2j** was also obtained in a quantitative yield under the standard conditions (entry 10). Alkyl diphenylphosphinites **1k-1o**, despite the different alkyl groups, all afforded the same H-phosphine oxide **2k** quantitatively (entries 11-15).

As shown in Table 3 (right column), the new TfOH-catalyzed rearrangement of **1** to selectively afford the corresponding C-P(O) compounds **3** in the absence of water is also a rather general method for the synthesis of alkylphosphonates and a variety of phosphites could efficiently convert under the mild reaction conditions to produce the corresponding C-P(O) compounds **3** in good to excellent yields. Thus, substrates with methyl, ethyl, *n*-butyl, allyl, benzyl groups all gave the corresponding alkylphosphonates in high yields under the standard solvent-free conditions (Table 3, right column, entries 2-6). Different to the reaction in the presence of water, the PhO group was found inert under this water-free condition (entry 9). Thus, contrary to the reactions

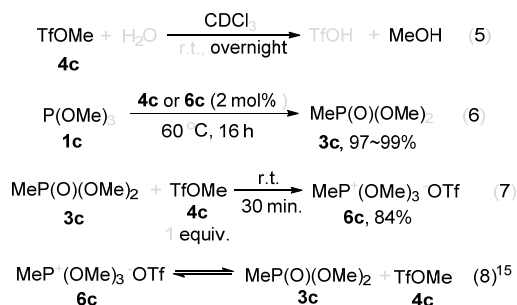
with water that generated mixtures, without water, unsymmetrical phosphites **1g** and **1h** both underwent C-O cleavage at the MeO moiety selectively and gave phosphonates **3g** and **3h** in high yields (entries 7 and 8). Selective transformation was also achieved with substrates having both bulky and small alkoxy groups, i.e., the reactions of **1q** and **1r** selectively occurred at the smaller MeO group, affording the corresponding Me-P(O) phosphonates **3q** and **3r** in satisfactory yields, respectively (entries 17-18). Similarly, phosphinate **3j** and a variety of phosphine oxides **3k-3p** were also obtained under similar conditions. Most likely due to the greater steric hindrance generated in the rearrangement process (*vide infra*), the reactions of bulky triisopropyl phosphite (**1a**) and phosphinites (**1m** and **1o**) were less efficient and gave lower yields of the products (entries 1, 13, 15).

Synthetic usefulness of the current method is also apparent. As shown in eq. 2,¹² in a 100 gram scale reaction of P(OMe)₃ (**1c**) with water, even with the catalyst loading lowered to 0.1 mol% only, the reaction is still very efficient, ensuring full conversion of **1c** to afford the corresponding **2c** in 93% isolated yield. Although the limit of the low catalyst loading is not determined at present, the high reaction efficiency clearly demonstrated the usefulness and potential practical application of the method in industrial scale manufacturing.

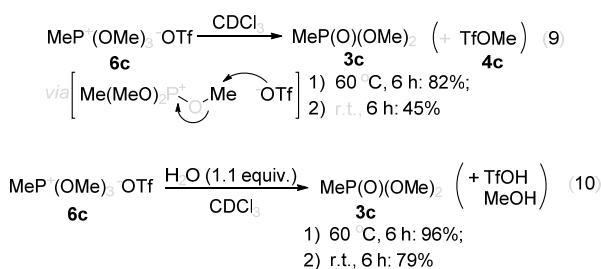


On the other hand, to probe the reaction mechanism, control reactions were then conducted.¹² Firstly, treatment of P(OMe)₃ (**1c**) with 1 equiv. of TfOH quickly generated 99% yield of HP(O)(OMe)₂ (**2c**) and also TfOMe (**4c**) (eq. 3). This reaction very possibly proceeded, as supported by the literature, *via* formation of phosphonium salt HP⁺(OMe)₃⁻OTf (**5c**) by protonation of **1c** with TfOH,¹¹ followed by, without the participation of water,¹⁴ an intramolecular S_N2-type attack of TfO⁻ at a Me group of **5c** to give **2c** and TfOMe.^{11a-b} Then, the reaction of **4c** and **1c** in Et₂O quickly precipitated to afford another phosphonium salt MeP⁺(OMe)₃⁻OTf (**6c**) in 84% isolated yield (eq. 4, entry 1);^{11b,15} whereas, in the more soluble solvent CDCl₃, the reaction gave a lower yield of **6c** with generation of **3c** (eq. 4, entry 2), suggesting the conversion of **6c** to **3c** may be very fast (*vide infra*). **4c** Could

also easily hydrolyze in the presence of water (eq. 5). Interestingly, **4c** and **6c** could catalyze the model reaction efficiently to give almost quantitative yields of **3c** (eq. 6),¹⁶ suggesting an interesting mechanism that may involve TfOR (**4**) and $\text{RP}^+(\text{OR})_3\text{OTf}$ (**6**) as the active catalysts/intermediates. Moreover, product **3c** could also react with **4c** fastly to give a high yield of **6c** (eq. 7). This is consistent with the equilibrium between **3**, **4** and **6** as documented in the literature (eq. 8).¹⁵



Although Rumpf and Lewis have successively proposed a bimolecular mechanism (the autocatalytic mechanism with the P center of **1** working as the nucleophile) for the reaction of **1c** and **6c** based on the findings including that **6c** is relatively stable and slow in conversion to **3c**,¹⁵ we observed that conversion of pure **6c** to **3c** is rather fast (82%) even at room temperature (45%) (eq. 9, see also entry 2 of eq. 4). Without **1c**, this reaction possibly proceeded *via* a monomolecular mechanism involving the $\text{S}_{\text{N}}2$ -type attack of TfO^- at a Me group of **6c** (eq. 9, similar to the one shown in eq. 3), which, as Lewis commented, still exists even in bimolecular mechanism dominated reactions.¹⁵ The low conversion of **6c** to **3c** observed by Lewis¹⁵ is likely due to the equilibrium between **3c**, **4c**, and **6c** (eq. 8),¹⁷ which otherwise suggests that, if the equilibrium can be broken and driven rightward by removing **4c**, conversion of **6c** may be more efficient to afford higher yields of **3c**. Indeed, by adding 1.1 equiv. of water to remove **4c** through its hydrolysis (eq. 5), high yields of **3c** could be obtained (96%) even at room temperature (79%) (eq. 10). Based on these findings, the observed fast reaction of **1** and **6** may not come from their bimolecular reaction, but comes from the reaction of **1** and TfOR (**4**) released from the conversion of **6** to **3**, because, conversion of **6** to **3** can be very fast (entry 2 of eq. 4, and eqs. 9 and 10), and, the presence of **1** can effectively remove **4** from the equilibrium to give **6** (eq. 4), just as water can do (eq. 10). Therefore, these results support more the monomolecular mechanism.



In addition, owing to the bulkyness of both substrates, the bimolecular reaction of P(III) esters **1** with quaternary phosphonium salts **6** should also be sterically unfavoured. This speculation is consistent with experimental findings observed in substrate extension. For example, unsatisfactory results could only be obtained with sterically more bulky substrates (Table 3, right column, entries 1, 13, and 15); and, for substrates bearing both bulky and small alkoxy groups, the reaction selectively occurred at the smaller MeO group to give only the Me-P(O) products (entries 17-18).

To achieve more theoretical understanding on the reaction mechanism and further verify which the more possible path is, theoretical calculation of both the monomolecular and bimolecular transition states was performed.¹² As shown in Figure 1, preliminary theoretical calculation revealed that the energy barrier of the monomolecular transition state (**TS1**) is ca. 52.12 KJ/mol, which is ca. 5.5 KJ/mol lower than that of the bimolecular transition state (**TS2**, 57.66 KJ/mol). Clearly, the monomolecular **TS1** is more favoured than the bimolecular **TS2**. Therefore, the monomolecular mechanism should be more possible according to the preceding results of control reactions and bulky substrates, as well as the theoretical calculation of the possible transition states.

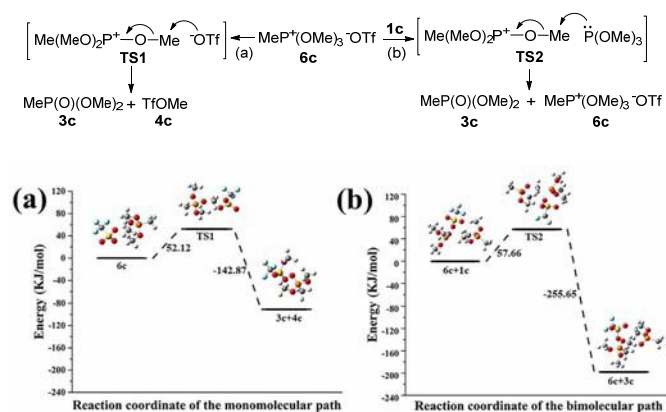
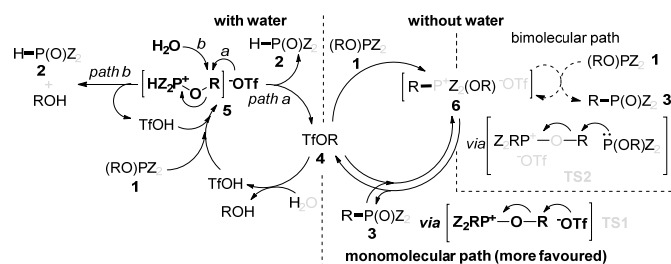


Figure 1. Theoretical Calculation of the Monomolecular and Bimolecular Transition States (Ball-and-stick representations. Atoms: red: oxygen; blue: fluorine; white: hydrogen; light yellow: sulfur; gray: carbon; orange: phosphorus): (a) The monomolecular path involving **TS1**; (b) The bimolecular path involving **TS2**.

Based on above results, we proposed a possible mechanism for the Brønsted acid-catalyzed C-O cleavage reactions of P(III) esters (Scheme 2). Thus, TfOH may firstly protonize (RO)PZ₂ to give a phosphonium salt $\text{H(RO)P}^+\text{Z}_2\text{OTf}$ (**5**).¹¹ Without water **5** may undergo C-O cleavage *via* a monomolecular $\text{S}_{\text{N}}2$ -type attack of TfO^- at the R group of **5** to give HP(O)Z_2 (**2**) and TfOR.^{11a-b} In the presence of water, TfOR may hydrolyze to regenerate TfOH (path a); or, at its formation, phosphonium salt **5** may directly react with water to give product **2**, byproduct ROH, and regenerate TfOH (path b), as TfO^- is a weak nucleophile and water can very possibly compete in this process.¹⁴ Then, the regenerated TfOH may be

recycled to catalyze the C-O cleaved hydrolysis of **1** to finally afford quantitative yields of HP(O)Z_2 (**2**).



Scheme 2. Proposed mechanism for the Brønsted acid-catalyzed C-O cleavage reactions of P(III) esters.

In the absence of water, once a catalytic amount of TfOR (ca. 2 mol% based on the 2 mol% TfOH added)¹⁸ is generated from the reaction of TfOH and $(\text{RO})\text{PZ}_2$ (**1**), it may further react with **1** to give a new phosphonium salt $\text{R-P}^+\text{Z}_2(\text{OR})\cdot\text{OTf}^-$ (**6**). According to preceding mechanistic findings, it is more likely that TfO^- will attack the RO moiety of **6** through a monomolecular $\text{S}_{\text{N}}2$ -type reaction to give C-O cleaved and rearranged R-P(O)Z_2 (**3**) and regenerate TfOR.²⁰ By further reacting with the remaining $(\text{RO})\text{PZ}_2$, TfOR works as the catalyst to drive the reaction forward to complete. In contrast, the bimolecular mechanism is less possible according to the experimental findings and preliminary theoretical calculation of **TS2**.

It should also be pointed out that the above monomolecular $\text{S}_{\text{N}}2$ -type mechanism may not be applied to all substrates.¹⁹ Clearly, for phosphites bearing an PhO group (Table 3, entries 7-9), the sp^2 Ph group cannot undergo $\text{S}_{\text{N}}2$ -type reactions with either TfO^- or water nucleophiles. Alternatively, the Ph-O bond may cleave first to give the product and a Ph^+ . For the same reason, $(\text{PhO})\text{PZ}_2$ cannot attack the Ph of TfOPh via $\text{S}_{\text{N}}2$ -type process to give the corresponding phosphonium salt. Hence, P(OPh)_3 (**1i**) could not afford the target product (Table 3, right column, entry 9) and the reactions of **1g-1h** selectively occurred at the MeO moiety to give **3g-3h** (Table 3, right column, entries 7-8).

Conclusions

In summary, water can determine the selectivity of the Brønsted acid-catalyzed C-O cleavage reactions of trialkyl phosphites: with water, the reaction occurs quickly at room temperature to afford quantitative yields of H-phosphonates; without water, the reaction selectively leads to the production of alkylphosphonates, demonstrating a mild and efficient halide-free alternative for the Michaelis-Arbuzov reaction. Mechanistic studies and the results of bulky substrates showed that the reaction perhaps takes place via a monomolecular mechanism. This method is general in substrate scope as it can be readily extended to phosphonites and phosphinites for preparation of the corresponding H-phosphinates, alkylphosphinates, H-phosphine oxides, and alkylphosphine oxides. This method can also be easily scaled up to 100 gram

reaction even with a much lower loading of the catalyst without affecting the reaction efficiency at all. All these clearly revealed the method's usefulness and potential practical utilities in industrial manufacturing.

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- The Michaelis-Arbuzov reaction of trialkyl phosphites with alkyl halides, is one of the most useful methods for the construction of C-P(O) bonds.⁵ However, drawbacks of this method such as the use of toxic alkyl halides, harsh conditions, heavy pollution, low efficiency, and release of toxic gas are also obvious. To solve the problems, modified methods have been developed.^{6,7} For example, trimethylsilyl Lewis acids were used to catalyze the Michaelis-Arbuzov rearrangement of trivalent phosphorus esters,⁶ but these methods either have a limited substrate scope or the used P(III) esters are not readily available. More recently, modified Michaelis-Arbuzov reactions using alcohols instead of alkyl halides have also been reported under ZnI_2 , ZnBr_2 , or PPh_3/DDQ -mediated conditions,⁷ but these methods generally require anhydrous conditions, stoichiometric amounts of activators, restricted to the more reactive allylic

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- 17 We also observed low conversions of **6c** to **3c** if **6c** prepared from P(OMe)₃ (**1c**) and TfOMe (**4c**) (eq. 4) was not isolated from the reaction mixture but directly used in the reactions of eq. 9.¹² This is because the reaction mixture contains considerable **4c** that can hinder conversion of **6c** to **3c**, by other words, react with **3c** to give **6c** (eq. 7).
- 18 Indeed, as shown in Tables 2 and 3, the yields of product R-P(O)₂ (**3**) are up to 98% yields.
- 19 We are thankful to one of the reviewers for this proper and helpful suggestion.
- 20 The observed lower reaction efficiency and low products' yields of the sterically more bulky substrates (Table 3, right column, entries 1, 13, and 15) that are consistent with the rules of the S_N2-type reactions may be another support to this mechanistic proposal.