

# **Studies on Catalytic PO–R Bond Cleavages Generating Phosphonates**

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# **Studies on Catalytic PO–R Bond Cleavages Generating Phosphonates**

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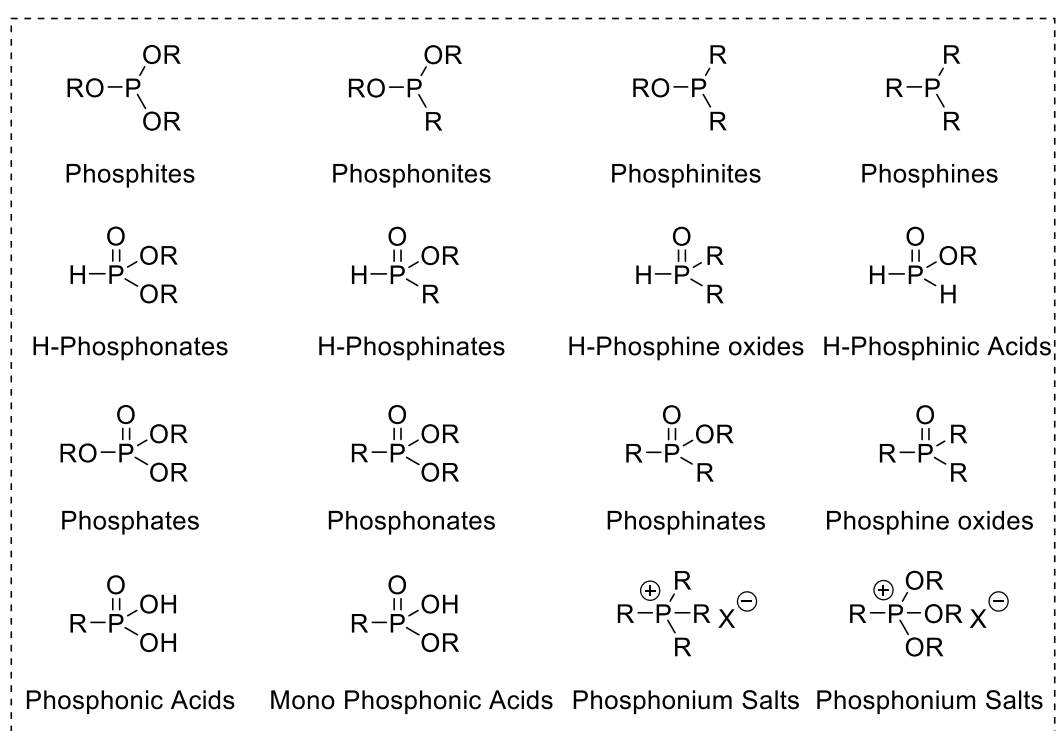
# Chapter 1

## General Introduction

### 1-1. Organophosphorus Compounds

Organophosphorus compounds consist of phosphorus element are important organic compounds. For example, the tricoordinated P(III) compounds such as phosphites, phosphines, tetracoordinated P(III) compounds like hydrogen-phosphonates, and tetracoordinated P(V) compounds such as phosphonates, phosphonic acids, phosphonium salts, are widely used in agricultural and medicinal chemistry, organic synthesis, catalysis, and functional materials (Scheme 1-1).<sup>1</sup>

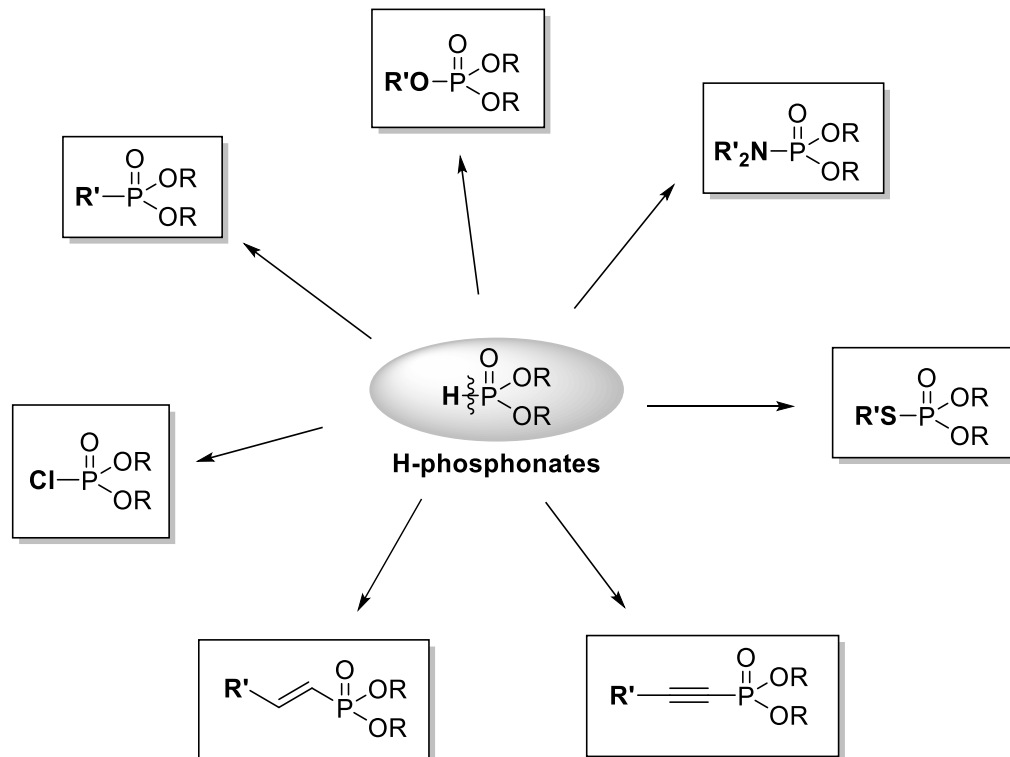
**Scheme 1-1.** Selected Examples of Organophosphorus Compounds



Among them, hydrogen-phosphonates are one of the most important synthetic precursors for organophosphorus compounds because the P(O)–H bonds can be transformed to various P(O)–Z (Z = C, N, O, X) bonds (Scheme 1-2).<sup>2</sup> For example, P(O)–R compounds can be synthesized by the famous Michaelis–Becker reaction of hydrogen-phosphonate with a base and followed by a nucleophilic substitution of phosphorus on a alkyl halide.<sup>2a</sup> In addition, our group have disclosed that the iron-catalyzed cross

dehydrogenative coupling reaction of alcohols with P(O)–H compounds which can produce high yields of the corresponding P(O)–O compounds. It also appears to be a rather general phosphorylation method and a variety of alcohols and P(O)–H compounds can be used as substrates in this coupling reaction.<sup>2b</sup> Our group have also developed a copper-catalyzed aerobic oxidative cross dehydrogenative coupling of amines with P(O)–H compounds leading to the P(O)–N bonds.<sup>2c</sup> Moreover, the dehydrogenative coupling reaction was also employed in the reaction of thiols with P(O)–H compounds via a Pd-catalyzed afforded the corresponding phosphorothioates.<sup>2d</sup> Alkynylphosphonates and alkenylphosphonates were prepared by the dehydrocoupling of alkynes and P(O)–H compounds in the presence of transition-metal catalyst.<sup>2e</sup> In addition, alkenylphosphonates could also be synthesized from the hydrophosphorylation of alkynes with P(O)–H compounds catalyzed by palladium.<sup>2f</sup> Atherton-Todd reaction can convert the P(O)–H bonds to produce the P(O)–Cl bond compounds in the presence of CCl<sub>4</sub>.<sup>2g</sup>

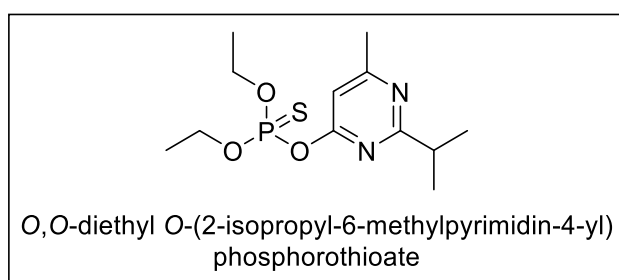
**Scheme 1-2.** Transformation of H-phosphonates to various P(O)–Z bond compounds



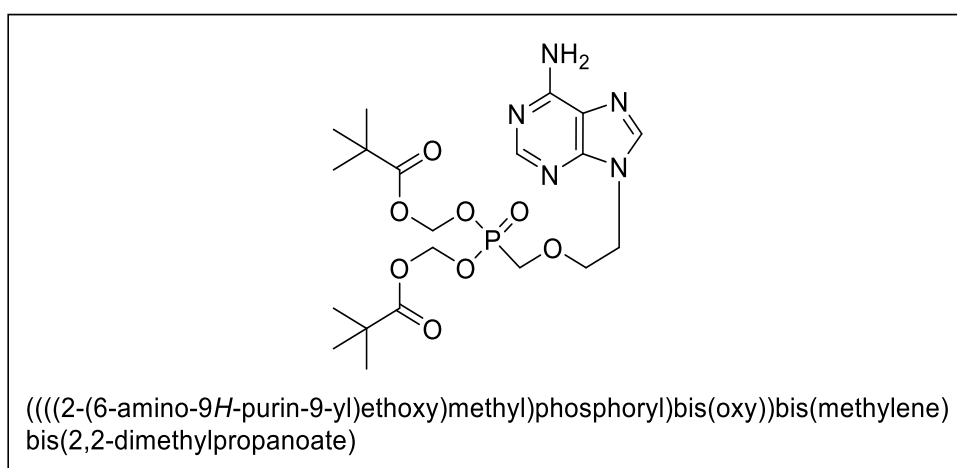
Due to the unique biological activities, phosphonates have a wide application in pesticides, medicines and flame retardants.<sup>3</sup> As shown in Figure 1-1, diazinon, *O,O*-diethyl *O*-(2-isopropyl-6-methylpyrimidin-4-yl)

phosphorothioate is one of the low-toxicity insecticides in common use.<sup>3a</sup> It has a very good effect on the control and eradication of pests on rice, corn, sugar cane and fruit trees. Adefovir dipivoxil, acyclic nucleoside phosphonate, is available for the treatment of DNA virus and retrovirus infections (Figure 1-2).<sup>3b</sup> It has been proven to be clinically effective and shows a broad spectrum of antiviral activity, as well as a unique mode of action, low drug resistance, controllable toxicity, and it is now available in an oral prodrug format. In 2013, Qian *et al.* reported a flame retardant monomer (DOPO-HEA) containing 9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide (DOPO) and unsaturated bonds (DOPO-HEA) (Figure 1-3).<sup>3c</sup> Due to its high phosphorus content, DOPO-HEA has excellent flame retardancy for epoxy acrylates.

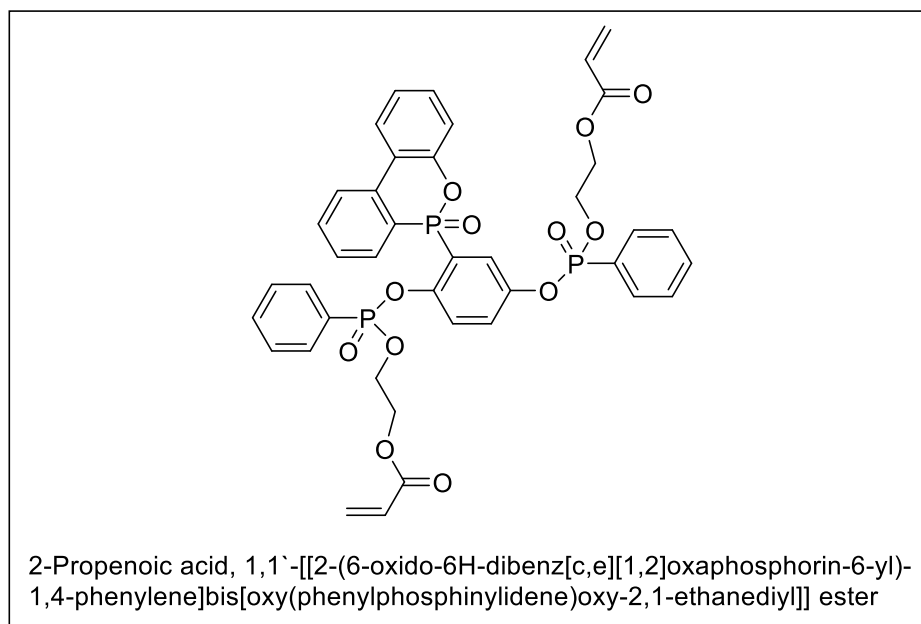
**Figure 1-1.** Diazinon



**Figure 1-2.** Adefovir dipivoxil (Bis(POM)-PMEA)

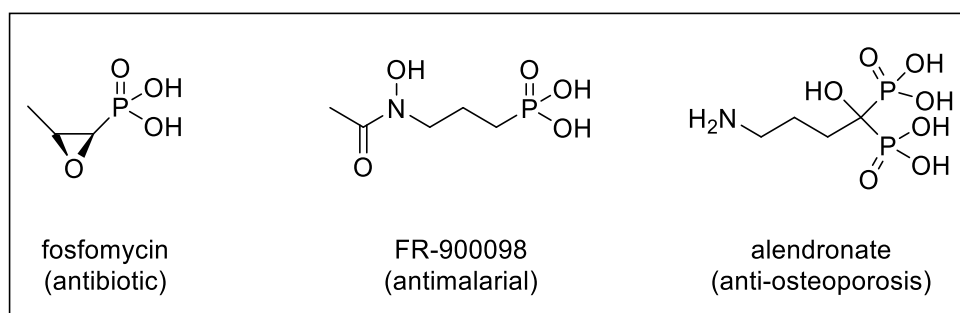


**Figure 1-3.** Flame retardant containing DOPO and active double bonds (DOPO-HEA)



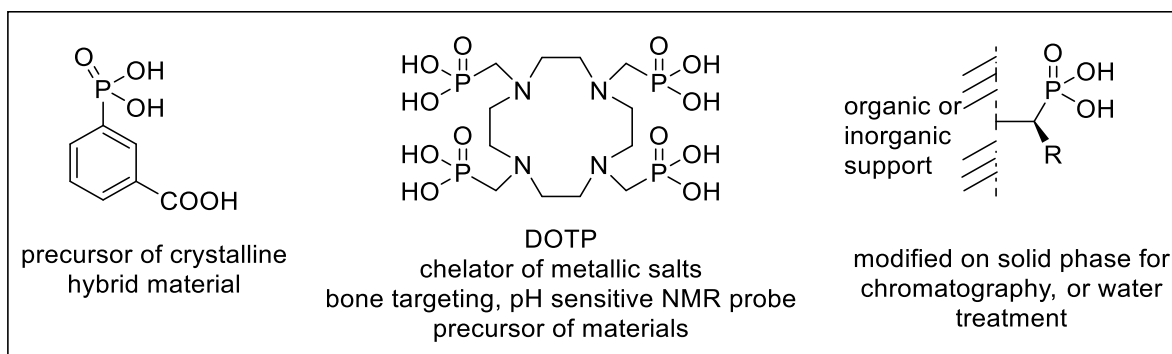
Phosphonic acids are an important class of compounds in medical and agricultural chemistry.<sup>4,1k</sup> For examples, fosfomycin is a clinically used antibiotic, FR-900098 is an antimalarial, and alendronate is a widely employed antiosteoporosis (Figure 1-4).<sup>5a-5c</sup> These phosphonic acids are also widely used in the preparation of hybrid functional materials, as exemplified in figure 1-5.<sup>5d-5f</sup>

**Figure 1-4.** Biomedicines



**Figure 1-5.** Hybrid functional materials

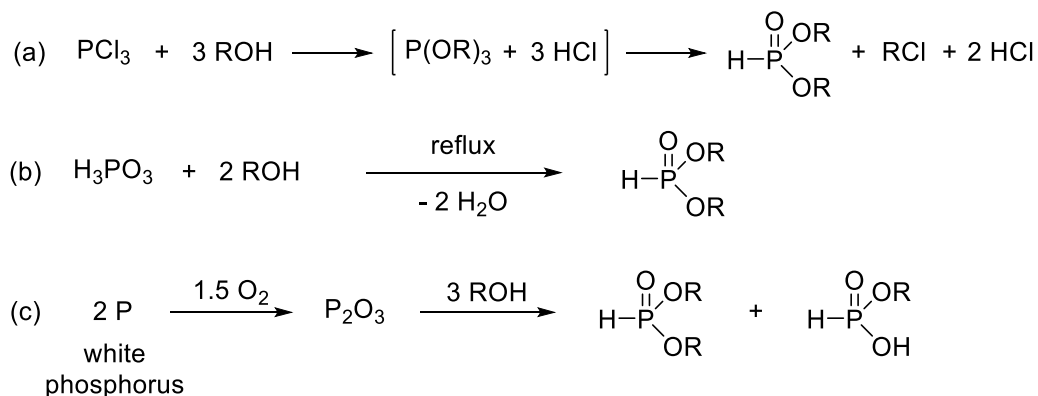




## 1-2. General Synthesis of Hydrogen-Phosphonates

The most common method (known as the McCombie process) to synthesize hydrogen-phosphonates is the reaction of phosphorous trichloride  $\text{PCl}_3$  with alcohols (Scheme 1-3a).<sup>6</sup> At about 0 °C, the reactions of an alcohol and phosphorus trichloride can lead to rapid stepwise alkoxylation at the phosphorus to give the trialkyl phosphites that are readily transformed to dialkyl H-phosphonates via dealkylation. This reaction can be performed in batch or continuous process. However, it inevitably produces large amounts of wastes. Saks *et al.* reported the preparation of dialkyl H-phosphonates from H-phosphonic acid  $\text{H}_3\text{PO}_3$  with alcohols (Scheme 1-3b).<sup>7</sup> However, this process required heating the mixture under reflux of a mixture of H-phosphonic acid and an excess of alcohols in order to obtain the dialkyl H-phosphonates. The water produced during the esterification also needs to be removed. As shown in Scheme 1-3c, hydrogen-phosphonates could also be synthesized from the oxidation of white phosphorus followed by treatment of the intermediate  $\text{P}_2\text{O}_3$  with alcohols.<sup>8</sup>

**Scheme 1-3.** Preparation of Hydrogen-Phosphonates

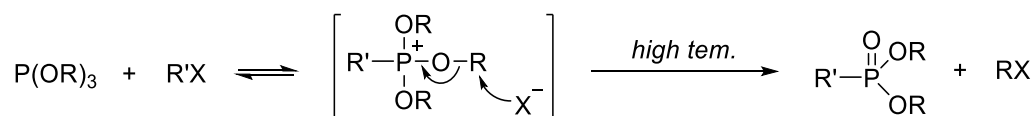


### 1-3. General Synthesis of Alkyl- and Arylphosphonates

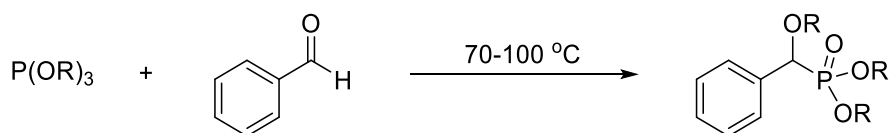
The famous Michaelis–Arbuzov reaction is the most popularly used for the preparation of alkylphosphonates (Scheme 1-4a).<sup>9</sup> This reaction is a reaction of trialkyl phosphites  $P(OR)_3$  with alkyl halides  $R'X$  at high temperatures to produce the alkyl-phosphonates and another alkyl halides  $RX$ . Trialkyl phosphites can also react with aldehydes to afford  $\alpha$ -hydroxy phosphonates (known as Abramov reaction) (Scheme 1-4b).<sup>10</sup> In addition, as shown in Scheme 1-4c, the Michaelis-Becker reaction is used to prepare the alkyl-phosphonates from dialkyl phosphites and alkyl halides  $R'X$  promoted by a base.<sup>10</sup>

**Scheme 1-4.** Preparation of Alkyl-Phosphonates

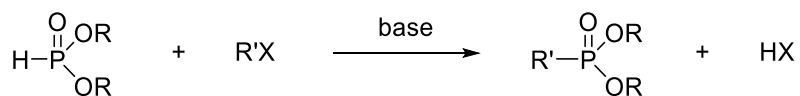
(a) Michaelis-Arbuzov reaction



(b) Abramov reaction



(c) Michaelis-Becker reaction

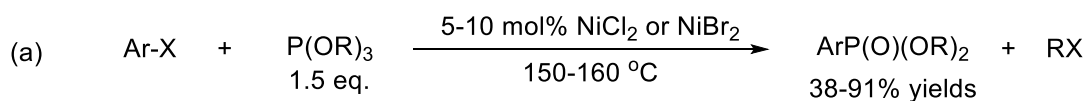


However, these mentioned methods (Scheme 1-4) are limited to the preparation of alkylphosphonates, and usually, transition-metals are required for synthesizing aryl-phosphonates from  $P(OR)_3$  and  $ArX$  ( $X = Cl, Br, I, NHNH_2$  etc.). For example, in 1970, Tavs published an important modification to the classic Michaelis-Arbuzov reaction. By using nickel catalysts, dialkyl arylphosphonate  $ArP(O)(OR)_2$  could be successfully prepared from a combination of  $(RO)_3P/ArX$  (Scheme 1-5a).<sup>11</sup> In 2011, Zhang reported the nickel-catalyzed phosphonylation of aryl triflates with triethyl phosphite under the promotion of the additive of  $KBr$ . This catalytic system first used aryl triflates in the nickel-catalyzed Arbuzov reaction (Scheme 1-5b).<sup>12</sup> As shown

in Scheme 1-5c, diphenyl arylphosphonates were also synthesized catalyzed by  $\text{NiCl}_2$ . This method is a nickel-catalyzed Arbuzov reaction, which relies on the assistance of triethyl phosphite  $\text{P}(\text{OEt})_3$ .<sup>13</sup> In 2014, Iranpoor group described a reusable palladium ( $\text{PdCl}_2$ ) catalyzed Arbuzov reaction of aryl iodides, bromides and chlorides with trialkylphosphites in water (Scheme 1-5d).<sup>14</sup> In this reaction, it is also demonstrated that tetrabutylammonium bromide can be used as the reducing agent for the generation of  $\text{Pd}(0)$  at room temperature. Moreover, the catalysts can be reused for several times.

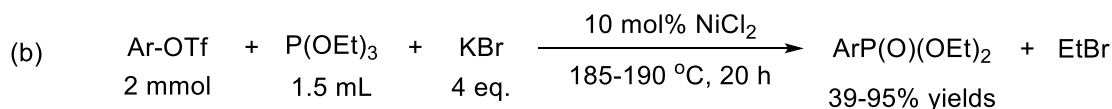
In addition, Cu was also applicable to catalyze the Arbuzov reaction to give the arylphosphonates. In 2014, Taillefer reported the copper-catalyzed ( $\text{CuI}$ ) Michaelis–Arbuzov reaction to prepare aryl phosphonates, aryl phosphinates, and aryl phosphine oxides from aryl iodides (Scheme 1-5e).<sup>15</sup> A  $\text{CuO}$ -catalyzed coupling reaction of trialkyl phosphites with arylhydrazines to afford the corresponding arylphosphonates was also developed (Scheme 1-5f).<sup>16</sup>

#### **Scheme 1-5.** Transition-Metal-Catalyzed Preparation of Aryl-Phosphonates

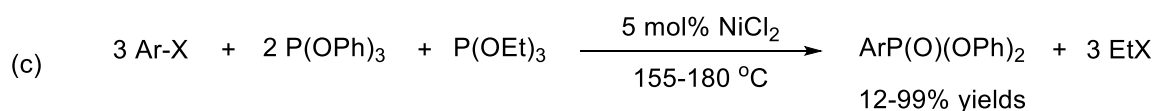


R = Me, Et, *i*-Pr; X = Br, Cl

Ar = Ph, 4-MePh, 4-MeOPh, 4-ClPh, Naphthyl-(1),(2), *etc.*

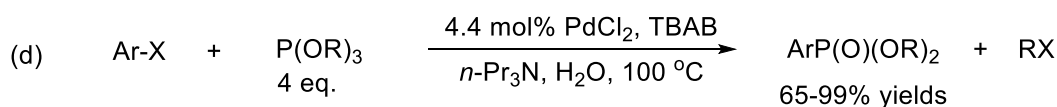


Ar = Ph, 4-MePh, 2-MePh, 3,4-MePh, 4-OMePh, 4-*t*-BuPh, 4-AcPh, 4-MeO<sub>2</sub>CPh, 1-naphthyl, 2-naphthyl, *etc.*



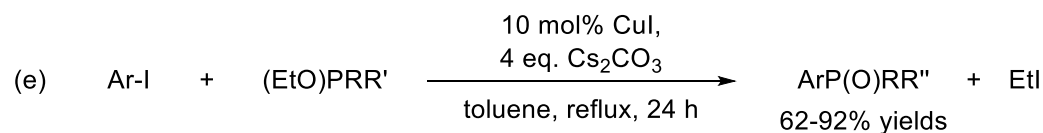
X = I, Br, Cl

Ar = Ph, 4-MePh, 4-OMePh, 4-BrPh, 4-ClPh, 4-EtO<sub>2</sub>CPh, *etc.*



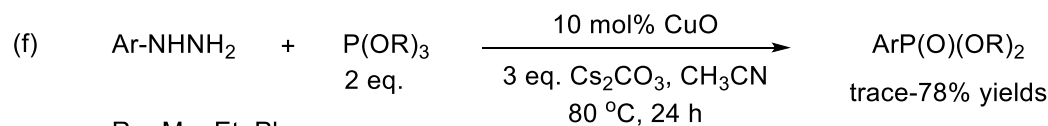
R = Et, *i*-Pr; X = I, Br, Cl

Ar = Ph, 4-MePh, 4-OMePh, 4-NitroPh, 4-CNPh, 4-CF<sub>3</sub>Ph, 2-MePh, 1-Naphtyl, 4-BrPh, 4-ClPh, *etc.*



R, R' = Et, Ph; R = OEt, R' = Ph

Ar = Ph, 4-MePh, 4-OMePh, 4-OHPh, 4-FPh, 4-ClPh, 4-BrPh, 4-IPh, 4-CNPh, *etc.*



R = Me, Et, Ph

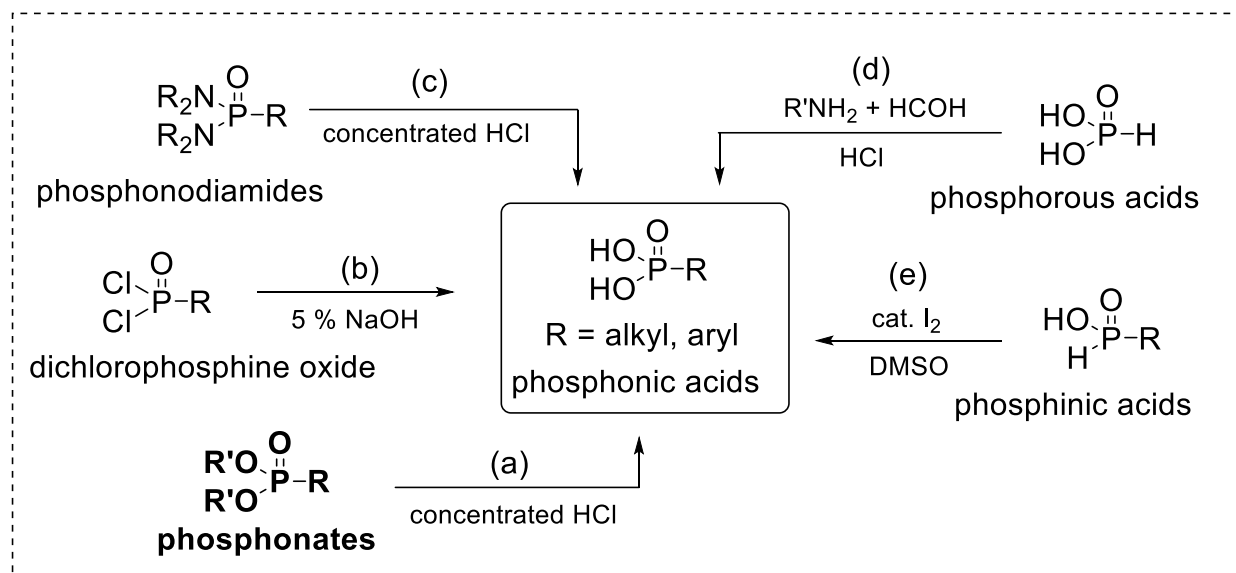
Ar = Ph, 4-MePh, 2-MePh, 4-OMePh, 4-*t*-BuPh, 4-FPh, 4-ClPh, 4-BrPh, 4-CNPh, 4-NO<sub>2</sub>Ph, *etc.*

## 1-4. General Synthesis of Phosphonic Acids

Phosphonic acids have attracted wide attention of many chemists due to the unique phosphonic acid functional group. Therefore, many methods have been developed to prepare phosphonic acids (Scheme 1-

6).<sup>1k,4a</sup> Phosphonic acids were most generally prepared by the hydrolysis of dialkyl phosphonates in hot concentrated hydrochloric acid (Scheme 1-6a).<sup>17</sup> The hydrolysis of dichlorophosphine oxides under basic conditions using aqueous sodium hydroxide (5% NaOH) could be produced the corresponding phosphonic acids (Scheme 1-6b).<sup>18</sup> Moreover, as shown in Scheme 1-6c, phosphonic acids especially aminophosphonic acids and nucleoside analogues were synthesized via the hydrolysis of phosphonodiamides using hot concentrated hydrochloric acid.<sup>19</sup> The direct methods using phosphorous acid ( $\text{H}_3\text{PO}_3$ ) can simultaneously generate phosphonic acids. The Moedritzer–Irani reaction, that was first reported in 1966, is the reaction of an primary or secondary amine, formaldehyde and phosphorous acid in acidic media (HCl), that can also produce the corresponding amino-bis(methylenephosphonic acid) (Scheme 1-6d).<sup>20</sup> In addition, phosphonic acids are also obtained from the oxidation of phosphinic acids in the presence of DMSO catalyzed by iodide (Scheme 1-6e).<sup>21</sup>

**Scheme 1-6.** Preparation of Phosphonic Acids



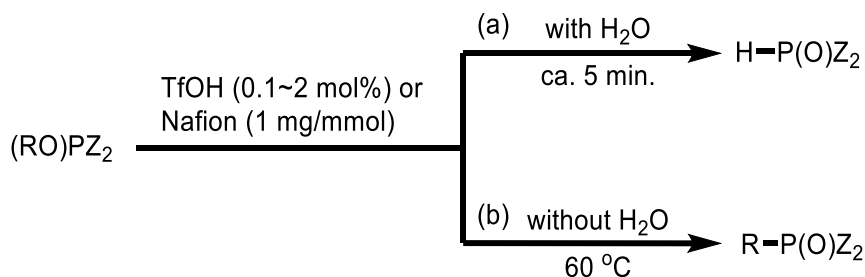
## 1-5. Survey of This Thesis

Having wide applications in organic synthesis, catalysis, agricultural & medicinal chemistry, and functional materials, organophosphorus compounds are highly useful chemicals. Despite the importance, general and

efficient methods for their synthesis are limited,<sup>22</sup> as heavy pollution associated with the industrial preparation of the organophosphorus compounds are notorious. Therefore, the development of practically useful, clean, and efficient methods for the preparation of organophosphorus compounds possesses great scientific and industrial importance. In this thesis, I have studied new methods for the preparation of hydrogen phosphonates  $\text{H-P(O)(OR)}_2$ , alkylphosphonates  $\text{R-P(O)(OR)}_2$ , arylphosphonates  $\text{Ar-P(O)(OAr)}_2$ , and phosphonic acids  $\text{RP(O)(OH)}_2$ , via catalytic cleavages of  $\text{PO-R}$  bonds of the commercially readily available starting chemicals (trialkyl phosphites, triaryl phosphites and phosphonates).

Chapter 2 describes the selectivity of Brønsted acid-catalyzed C–O cleavage reactions of trialkyl phosphites: in the presence of water, the reaction quickly takes place at room temperature to afford quantitative yields of H-phosphonates; in the absence of water, the reaction selectively affords alkylphosphonates in high yields, providing a novel halide-free alternative to the famous Michaelis-Arbuzov reaction (Scheme 1-7). 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. Nafion, a solid acid, also shows excellent catalytic activity in the reactions and can be recycled and reused without losing any activity at all, enabling a simple and rapid large-scale 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.

**Scheme 1-7.** Preparation of H- and alkylphosphonates

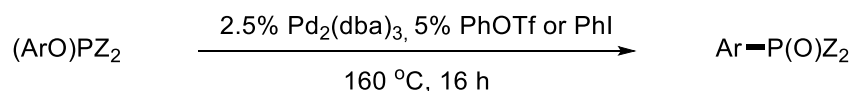


Michaelis-Arbuzov reaction, the formation of P(V) phosphonates  $\text{RP(O)(OR)}_2$  by the rearrangement of

P(III) phosphites via a combination of  $(\text{RO})_3\text{P/RX}$ , was discovered more than 120 years ago. However, it is limited to the generation of alkylphosphonates. Therefore, I further focus on the preparation of arylphosphonates.

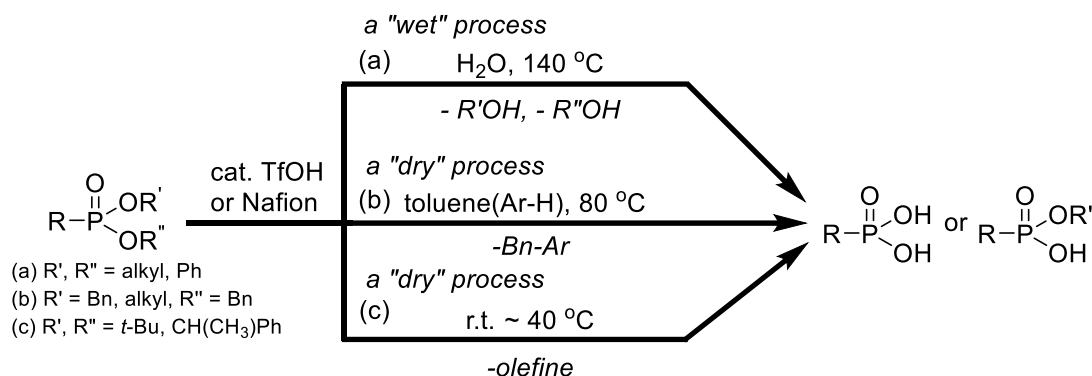
In Chapter 3, I developed an unprecedented simple Pd/ArX catalyst system that can efficiently catalyze the conversion of triaryl phosphites  $(\text{ArO})_3\text{P}$  to arylphosphonates  $\text{Ar-P(O)(OAr)}_2$  (Scheme 1-8). This an unprecedented palladium catalysed rearrangement can settle the historically long-unresolved last problem for the Michaelis–Arbuzov reaction and therefore complete it finally. This method is general in substrate scope as it can be readily extended to aryl phosphonites and phosphinites for synthesizing the corresponding aryl phosphinates and phosphine oxides.

**Scheme 1-8.** Preparation of arylphosphonates



In Chapter 4, I have also disclosed that the above obtained phosphonates (Chapter 2 and 3) can be further converted to the corresponding phosphonic acids catalyzed by Brønsted acid via PO–R cleavage under wet or dry processes (Scheme 1-9). Thus, in the presence of water, a range of alkyl-, alkenyl-, and aryl-substituted phosphonates can be generally hydrolyzed to the corresponding phosphonic acids in good yields catalyzed by trifluoromethyl sulfonic acid (TfOH) at 140 °C (the wet process). On the other hand, with specific substituents of the phosphonate esters, the conversion to the corresponding phosphonic acids can be achieved under milder conditions in the absence of water (the dry process). Thus, the conversion of dibenzyl phosphonates to the corresponding phosphonic acids took place smoothly at 80 °C in toluene or benzene in high yields. Moreover, selective conversion of benzyl phosphonates  $\text{RP(O)(OR') (OBn)}$  to the corresponding mono phosphonic acids  $\text{RP(O)(OR') (OH)}$  can also be achieved under the reaction conditions. The dealkylation via the generation of isobutene of *di**tert*-butyl phosphonate, and the related catalysis by TfOH took place even at room temperature to give the corresponding phosphonic acids in good to high yields. Nafion also shows high catalytic activity for these reactions. By using Nafion as the catalyst, phosphonic acids could be easily prepared on a large scale via a simple process.

### Scheme 1-9. Preparation of phosphonic acids



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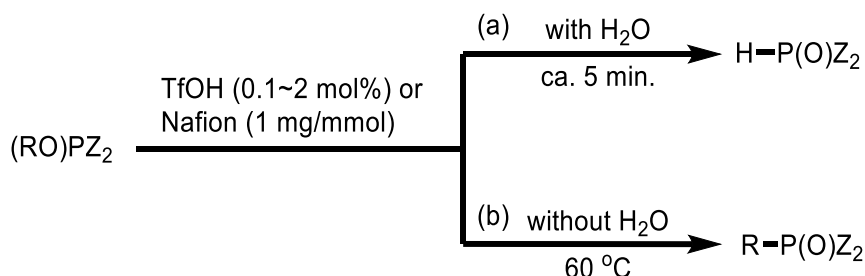
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## Chapter 2

# Brønsted Acid-Catalyzed PO–R Cleavage of P(III) Esters Selectively Producing P(O)–H and P(O)–R Compounds

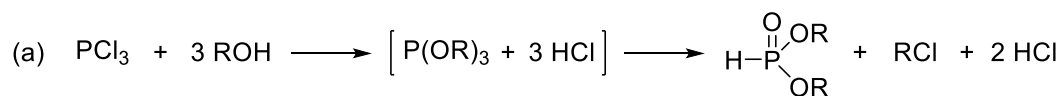
### Abstract

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.

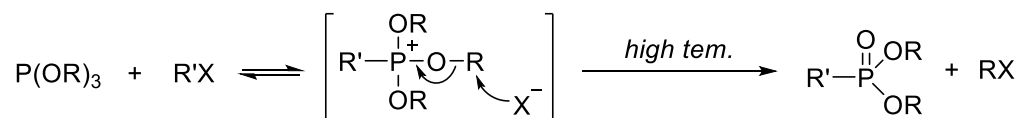


### 2-1. Introduction

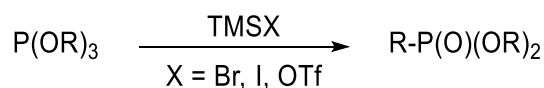
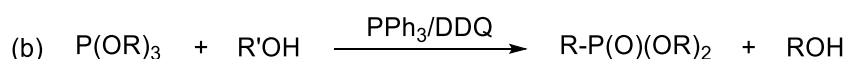
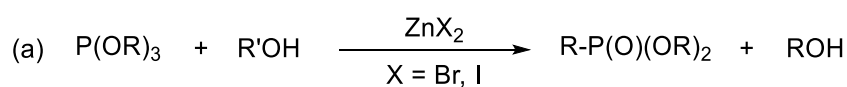
Hydrogen phosphonates  $H-P(O)(OR)_2$  and substituted phosphonates  $R-P(O)(OR)_2$  are two industrially important chemicals. Conventionally, hydrogen phosphonates  $H-P(O)(OR)_2$  were prepared from the reaction of  $PCl_3$  and  $ROH$  (Scheme 2-1a), which inevitably produces large amounts of wastes.<sup>1</sup> Alkylphosphonates  $R-P(O)(OR)_2$  were prepared from  $(RO)_3P$  with  $RX$  (the Michaelis-Arbuzov reaction) under high temperatures (Scheme 2-1b).<sup>2</sup>

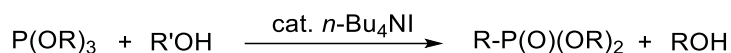
**Scheme 2-1.** Traditional methods for preparing H- and alkylphosphonates

(b) Michaelis-Arbuzov reaction



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. 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.<sup>3-5</sup> For example, trimethylsilyl Lewis acids were used to catalyze the Michaelis–Arbuzov rearrangement of trivalent phosphorus esters (Scheme 2-2),<sup>3</sup> 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  $\text{ZnI}_2$ ,  $\text{ZnBr}_2$ , or  $\text{PPh}_3/\text{DDQ}$ -mediated conditions (Scheme 2-3),<sup>4</sup> but these methods generally require anhydrous conditions, stoichiometric amounts of activators, restricted to the more reactive allylic and benzyl alcohols, and can generate large amounts of wastes. Recently, our group reported an efficient modified Michaelis–Arbuzov reactions using  $n\text{Bu}_4\text{NI}$  (*n*-butylammonium iodide) as catalyst (Scheme 2-4).<sup>5</sup>

**Scheme 2-2.** TMSX-catalyzed Michaelis–Arbuzov rearrangements**Scheme 2-3.**  $\text{ZnX}_2$  or  $\text{PPh}_3/\text{DDQ}$ -mediated Michaelis–Arbuzov reactions

**Scheme 2-4.** Modified Michaelis–Arbuzov reactions using alcohols instead of alkyl halides**2-2. Brønsted Acid-Catalyzed C–O Cleavage of P(OR)<sub>3</sub> in the Presence of Water****2-2-1. Optimization of Reaction Conditions**

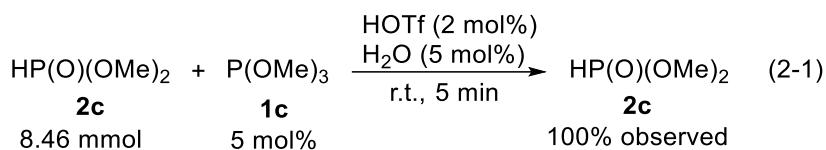
During the investigation on the reactions of P(III) esters,<sup>5</sup> we observed that direct addition of a Brønsted acid to the commercial triisopropyl phosphite (**1a**) could lead to the generation of H-phosphonate HP(O)(Oi-Pr)<sub>2</sub> (**2a**) in variant yields. As shown in Table 2-1, 26% **2a** was obtained from a neat mixture of **1a** and water in the presence of only 2 mol% Ph<sub>2</sub>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.<sup>6</sup> Then, a variety of Brønsted acids were evaluated (entries 3–4), among which the perfluorinated sulfonic acids such as CF<sub>3</sub>CO<sub>2</sub>H, TfOH, *n*-C<sub>4</sub>F<sub>9</sub>SO<sub>3</sub>H, and *n*-C<sub>8</sub>F<sub>17</sub>SO<sub>3</sub>H ensured rapid and complete hydrolysis of **1a** at room temperature to afford quantitative yields of **2a** by 5 min (entry 3).<sup>6</sup> However, the catalytic activity is low with other Brønsted acids such as AcOH, PhCO<sub>2</sub>H, and PhSO<sub>3</sub>H (entry 4).

**Table 2-1.** Brønsted acid-catalyzed C–O cleavage of P(Oi-Pr)<sub>3</sub> in the presence of H<sub>2</sub>O<sup>a</sup>

$\text{P(Oi-Pr)}_3 \xrightarrow[\text{r.t., 5 min}]{\text{cat. (2 mol\%), H}_2\text{O (1 equiv.)}} \text{H-P(O)(Oi-Pr)}_2$ <div style="display: flex; justify-content: space-around; width: 100%;"> <span><b>1a</b></span> <span><b>2a</b></span> </div>		
entry	cat. (2 mol%)	<b>2a</b> % <sup>b</sup>
1	Ph <sub>2</sub> P(O)OH	26
2	none	none
3	CF <sub>3</sub> CO <sub>2</sub> H, TfOH, <i>n</i> -C <sub>4</sub> F <sub>9</sub> SO <sub>3</sub> H, <i>n</i> -C <sub>8</sub> F <sub>17</sub> SO <sub>3</sub> H	>99 (94)
4	AcOH, PhCO <sub>2</sub> H, PhSO <sub>3</sub> H	7~10

<sup>a</sup> Reaction conditions: **1a** (2.3 mmol), H<sub>2</sub>O (1 equiv.), and catalyst (2 mol%) were mixed under air in an NMR tube at room temperature. The tube was sealed, shaken slightly, and subjected to NMR measurement in 5 min. <sup>b</sup> Yields based on <sup>31</sup>P NMR analysis (isolated yields were shown in parenthesis).

Worthy of mentioning is that, HP(O)(OR)<sub>2</sub> are currently mostly prepared by reacting PCl<sub>3</sub> with alcohols.<sup>1</sup> However, since P(OR)<sub>3</sub> formation is inevitable and difficult to remove, HP(O)(OR)<sub>2</sub> are generally contaminated with a small amount of P(OR)<sub>3</sub>. Therefore, the present reaction provides a total solution to this long-unsolved problem. For example, as shown in eq. 2-1, after treated with 2 mol% TfOH, the 5 mol% contaminant P(OMe)<sub>3</sub> (**1c**) in HP(O)(OMe)<sub>2</sub> (**2c**) could be completely converted into **2c**, providing a practical method for preparation of highly pure HP(O)(OR)<sub>2</sub> (**2**) by vacuum distillation.<sup>7</sup> 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.<sup>8</sup>



## 2-2-2. Scope of Substrates

The simplest TfOH was then chosen as the catalyst for substrate extension (Table 2-2). In the presence of water, 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 phosphite **1g** (entry 7), the observed unexpected C–O cleavage of the PhO group inspired us to investigate the reaction of triary phosphites such as P(OPh)<sub>3</sub>. Pleasingly, the otherwise difficult-to-prepare HP(O)(OPh)<sub>2</sub> (**2i**) could easily be obtained quantitatively from the readily available P(OPh)<sub>3</sub> under the standard conditions (entry 8). This method could also be readily extended to phosphonites and phosphinites to prepare the corresponding H-phosphinates and H-phosphine oxides (entries 9-15). Thus, H-phosphinate **2j** was also obtained in a

quantitative yield under the standard conditions (entry 9). Alkyl diphenylphosphinites **1k-1o**, despite the different alkyl groups, all afforded the same H-phosphine oxide **2k** quantitatively (entries 10-14). Similarly, dicyclohexylphosphine oxide **2p** was obtained in quantitative yield (entry 15).

**Table 2-2.** Substrate scope for TfOH-catalyzed C–O cleavage reactions of (RO)PZ<sub>2</sub> in the presence of H<sub>2</sub>O<sup>a</sup>

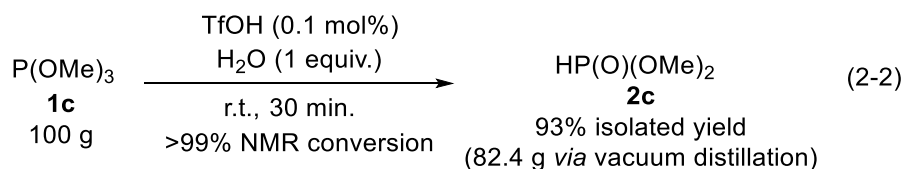
	$\begin{array}{c} \text{(RO)PZ}_2 \\ \mathbf{1} \end{array}$	$\xrightarrow[\text{r.t., 30 min}]{\text{TfOH (2 mol\%), H}_2\text{O (1 equiv.)}}$	$\begin{array}{c} \text{H}-\text{P(O)Z}_2 \\ \mathbf{2} \end{array}$
entry	(RO)PZ <sub>2</sub> ( <b>1</b> )	HP(O)Z <sub>2</sub> ( <b>2</b> )% <sup>b</sup>	
1	P(Oi-Pr) <sub>3</sub> ( <b>1a</b> )	HP(O)(Oi-Pr) <sub>2</sub> ( <b>2a</b> ): >99 (94)	
2	P(OEt) <sub>3</sub> ( <b>1b</b> )	HP(O)(OEt) <sub>2</sub> ( <b>2b</b> ): >99 (93)	
3	P(OMe) <sub>3</sub> ( <b>1c</b> )	HP(O)(OMe) <sub>2</sub> ( <b>2c</b> ): >99 (92)	
4	P(On-Bu) <sub>3</sub> ( <b>1d</b> )	HP(O)(On-Bu) <sub>2</sub> ( <b>2d</b> ): >99 (92)	
5	P(Oally) <sub>3</sub> ( <b>1e</b> )	HP(O)(Oally) <sub>2</sub> ( <b>2e</b> ): >99 (91)	
6	P(OCH <sub>2</sub> Ph) <sub>3</sub> ( <b>1f</b> )	HP(O)(OCH <sub>2</sub> Ph) <sub>2</sub> ( <b>2f</b> ): >99 (88)	
7	(MeO) <sub>2</sub> P(OPh) ( <b>1g</b> )	HP(O)(OMe) <sub>2</sub> ( <b>2c</b> ): 70 (50) HP(O)(OMe)(OPh) ( <b>2g</b> ): 30	
8	P(OPh) <sub>3</sub> ( <b>1i</b> )	HP(O)(OPh) <sub>2</sub> ( <b>2i</b> ): >99 (91)	
9	(MeO) <sub>2</sub> PPh ( <b>1j</b> )	HP(O)(OMe)Ph ( <b>2j</b> ): >99 (92)	
10	(MeO)PPh <sub>2</sub> ( <b>1k</b> )	HP(O)Ph <sub>2</sub> ( <b>2k</b> ): >99 (90)	
11	(EtO)PPh <sub>2</sub> ( <b>1l</b> )	HP(O)Ph <sub>2</sub> ( <b>2k</b> ): >99	
12	(i-PrO)PPh <sub>2</sub> ( <b>1m</b> )	HP(O)Ph <sub>2</sub> ( <b>2k</b> ): >99	
13	(PhCH <sub>2</sub> O)PPh <sub>2</sub> ( <b>1n</b> )	HP(O)Ph <sub>2</sub> ( <b>2k</b> ): >99	
14	PhCH(CH <sub>3</sub> )OPPh <sub>2</sub> ( <b>1o</b> )	HP(O)Ph <sub>2</sub> ( <b>2k</b> ): >99	
15	(MeO)PCy <sub>2</sub> ( <b>1p</b> )	HP(O)Cy <sub>2</sub> ( <b>2p</b> ): >99 (91)	

<sup>a</sup> Reaction conditions: **1** (2.3 mmol), H<sub>2</sub>O (1 equiv.), and catalyst (2 mol%) were mixed under air in an NMR tube at room temperature. The tube was sealed, shaken slightly, and subjected to NMR measurement in 30 min. <sup>b</sup> Yields based on <sup>31</sup>P NMR (isolated yields were shown in parenthesis).

### 2-2-3. Large Scale Reaction



Synthetic usefulness of the current method is also apparent. As shown in eq. 2-2, in a 100 gram scale reaction of P(OMe)<sub>3</sub> (**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.



## 2-3. Brønsted Acid-Catalyzed C–O Cleavage of P(OR)<sub>3</sub> in the Absence of Water

### 2-3-1. Optimization of Reaction Conditions

Very surprisingly, in sharp contrast to above results, *in the absence of water*, the C–O bond cleavage also occur with P(OR)<sub>3</sub> but selectively led to Michaelis–Arbuzov rearrangement products **3** (Table 2-3). As mentioned above, compounds **3** have long been prepared by the legendary Michaelis–Arbuzov reaction.<sup>2</sup> 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,<sup>2</sup> great efforts have been devoted to develop alternative ways that can efficiently and selectively afford the products under mild conditions.<sup>3-5</sup> To the best of our knowledge, the present Brønsted acid-catalyzed mild Michaelis–Arbuzov rearrangement of P(OR)<sub>3</sub> 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.<sup>3-5</sup> 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)<sub>3</sub> (**1b**) was treated with perfluorinated sulfonic acids under the same solvent-free condition, high yields of rearranged EtP(O)(OEt)<sub>2</sub> (**3b**) were obtained at 60 °C (Table 2-3, 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)<sub>3</sub> could give the corresponding phosphonate MeP(O)(OMe)<sub>2</sub> (**3c**) even at room temperature (entry 6).

**Table 2-3.** Brønsted acid-catalyzed C–O cleavage of P(OR)<sub>3</sub> in the absence of H<sub>2</sub>O<sup>a</sup>

	$\text{P(OR)}_3$ <b>1</b>	$\xrightarrow[\text{T, t}]{\text{cat. (2 mol\% ), anhydrous condition}}$	$\text{R-P(O)(OR)}_2$ <b>3</b>	
entry	<b>1</b> : $\text{P(OR)}_3$	cat. (2 mol%)	T, t	<b>3</b> : yield (%) <sup>b</sup>
1	<b>1b</b> : $\text{P(OEt)}_3$	TfOH	60 °C,16 h	<b>3b</b> : 98 (96)
2	<b>1b</b>	<i>n</i> -C <sub>4</sub> F <sub>9</sub> SO <sub>3</sub> H	60 °C,16 h	<b>3b</b> : 96
3	<b>1b</b>	<i>n</i> -C <sub>8</sub> F <sub>17</sub> SO <sub>3</sub> H	60 °C,16 h	<b>3b</b> : 93
4	<b>1b</b>	none	60 °C, 16 h	<b>3b</b> : none
5	<b>1b</b>	other acids <sup>c</sup>	60 °C, 16 h	<b>3b</b> : none
6 <sup>d</sup>	<b>1c</b> : $\text{P(OMe)}_3$	TfOH	r.t., 6 h	<b>3c</b> : 96 (95)

<sup>a</sup> Reaction conditions: P(OEt)<sub>3</sub> (2.3 mmol) and catalyst (2 mol%) were heated under N<sub>2</sub> in a glass tube (10 mL). <sup>b</sup> GC yields using decane as the internal standard (isolated yields were given in parenthesis). <sup>c</sup> AcOH, CF<sub>3</sub>CO<sub>2</sub>H, PhCO<sub>2</sub>H, Ph<sub>2</sub>P(O)OH, and PhSO<sub>3</sub>H were tested. <sup>d</sup> P(OMe)<sub>3</sub> (3.4 mmol) was used instead.

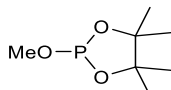
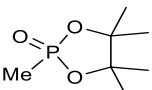
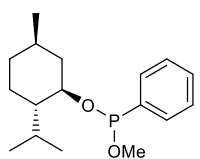
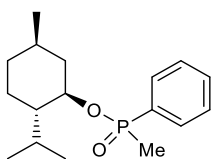
### 2-3-2. Scope of Substrates

As shown in Table 2-4, 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 (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).

**Table 2-4.** Substrate scope for TfOH-catalyzed C-O cleavage reactions of (RO)PZ<sub>2</sub> in the absence of water<sup>a</sup>

	$\begin{array}{c} \text{(RO)PZ}_2 \\ \mathbf{1} \end{array} \xrightarrow[60\text{ }^\circ\text{C, 16 h}]{\text{TfOH (2 mol\%), anhydrous condition}} \begin{array}{c} \text{R-P(O)Z}_2 \\ \mathbf{3} \end{array}$	
entry	(RO)PZ <sub>2</sub> ( <b>1</b> )	RP(O)Z <sub>2</sub> ( <b>3</b> )% <sup>b</sup>
1	P(Oi-Pr) <sub>3</sub> ( <b>1a</b> )	<i>i</i> -PrP(O)(Oi-Pr) <sub>2</sub> ( <b>3a</b> ): 15 <sup>c</sup>
2	P(OEt) <sub>3</sub> ( <b>1b</b> )	EtP(O)(OEt) <sub>2</sub> ( <b>3b</b> ): 96
3	P(OMe) <sub>3</sub> ( <b>1c</b> )	MeP(O)(OMe) <sub>2</sub> ( <b>3c</b> ): 95
4	P(On-Bu) <sub>3</sub> ( <b>1d</b> )	<i>n</i> -BuP(O)(On-Bu) <sub>2</sub> ( <b>3d</b> ): 85
5	P(Oally) <sub>3</sub> ( <b>1e</b> )	allyP(O)(Oally) <sub>2</sub> ( <b>3e</b> ): 94
6	P(OCH <sub>2</sub> Ph) <sub>3</sub> ( <b>1f</b> )	PhCH <sub>2</sub> P(O)(OCH <sub>2</sub> Ph) <sub>2</sub> ( <b>3f</b> ): 76
7	(MeO) <sub>2</sub> P(OPh) ( <b>1g</b> )	MeP(O)(OMe)(OPh) ( <b>3g</b> ): 83
8	(MeO)P(OPh) <sub>2</sub> ( <b>1h</b> )	MeP(O)(OPh) <sub>2</sub> ( <b>3h</b> ): 82
9	P(OPh) <sub>3</sub> ( <b>1i</b> )	--
10	(MeO) <sub>2</sub> PPh ( <b>1j</b> )	MeP(O)(OMe)Ph ( <b>3j</b> ): 95
11	(MeO)PPh <sub>2</sub> ( <b>1k</b> )	MeP(O)Ph <sub>2</sub> ( <b>3k</b> ): 93
12	(EtO)PPh <sub>2</sub> ( <b>1l</b> )	EtP(O)Ph <sub>2</sub> ( <b>3l</b> ): 80 <sup>d</sup>
13	( <i>i</i> -PrO)PPh <sub>2</sub> ( <b>1m</b> )	<i>i</i> -PrP(O)Ph <sub>2</sub> ( <b>3m</b> ): <10 <sup>c</sup>
14	(PhCH <sub>2</sub> O)PPh <sub>2</sub> ( <b>1n</b> )	PhCH <sub>2</sub> P(O)Ph <sub>2</sub> ( <b>3n</b> ): 92
15	PhCH(CH <sub>3</sub> )OPPh <sub>2</sub> ( <b>1o</b> )	PhCH(CH <sub>3</sub> )P(O)Ph <sub>2</sub> ( <b>3o</b> ): 36 <sup>c</sup>

16	(MeO)PCy <sub>2</sub> ( <b>1p</b> )	MeP(O)Cy <sub>2</sub> ( <b>3p</b> ): 92 <sup>e</sup>
17	 ( <b>1q</b> )	 ( <b>3q</b> ): 92
18	 ( <b>1r</b> )	 ( <b>3r</b> ): 65

<sup>a</sup> Reaction conditions: P(OEt)<sub>3</sub> (2.3 mmol) and catalyst (2 mol%) were heated under N<sub>2</sub> in a glass tube (10 mL). <sup>b</sup> Isolated yields. <sup>c</sup> Complex reaction occurred with generation of byproducts. <sup>d</sup> 100 °C. <sup>e</sup> 0.56 mmol (MeO)PCy<sub>2</sub> in 0.5 mL toluene was heated at 100 °C.

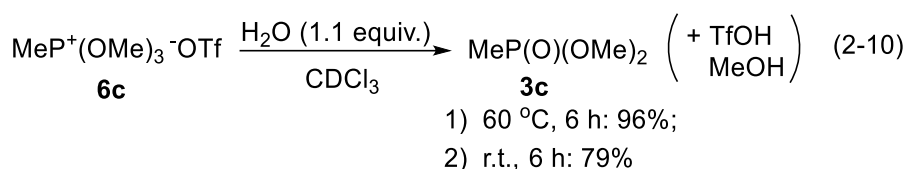
## 2-4. Mechanistic Studies

### 2-4-1. Control Experiments

To probe the reaction mechanism, control reactions were then conducted. Firstly, treatment of P(OMe)<sub>3</sub> (**1c**) with 1 equiv. of TfOH quickly generated 99% yield of HP(O)(OMe)<sub>2</sub> (**2c**) and also TfOMe (**4c**) (eq. 2-3). This reaction very possibly proceeded, as supported by the literature, *via* formation of phosphonium salt HP<sup>+</sup>(OMe)<sub>3</sub>·OTf (**5c**) by protonation of **1c** with TfOH,<sup>6</sup> followed by, without the participation of water,<sup>9</sup> an intramolecular S<sub>N</sub>2-type attack of TfO<sup>-</sup> at a Me group of **5c** to give **2c** and TfOMe.<sup>6a-b</sup> Then, the reaction of **4c** and **1c** in Et<sub>2</sub>O quickly precipitated to afford another phosphonium salt MeP<sup>+</sup>(OMe)<sub>3</sub>·OTf (**6c**) in 84% isolated yield (eq. 4, entry 1);<sup>6b,10</sup> whereas, in the more soluble solvent CDCl<sub>3</sub>, the reaction gave a lower yield of **6c** with generation of **3c** (eq. 2-4, 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. 2-5). Interestingly, **4c** and **6c** could catalyze the model reaction efficiently to give almost quantitative yields of **3c** (eq. 2-6),<sup>11</sup> suggesting an interesting mechanism that may involve TfOR (**4**) and RP<sup>+</sup>(OR)<sub>3</sub>·OTf (**6**) as the active catalysts/intermediates. Moreover, product **3c** could also react with **4c** fastly to give a high yield of **6c** (eq. 2-7). This is consistent with the equilibrium between **3**, **4** and **6** as documented in the literature (eq. 2-8).<sup>10</sup>

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**,<sup>10</sup> we observed that conversion of

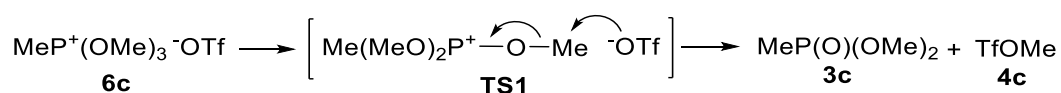


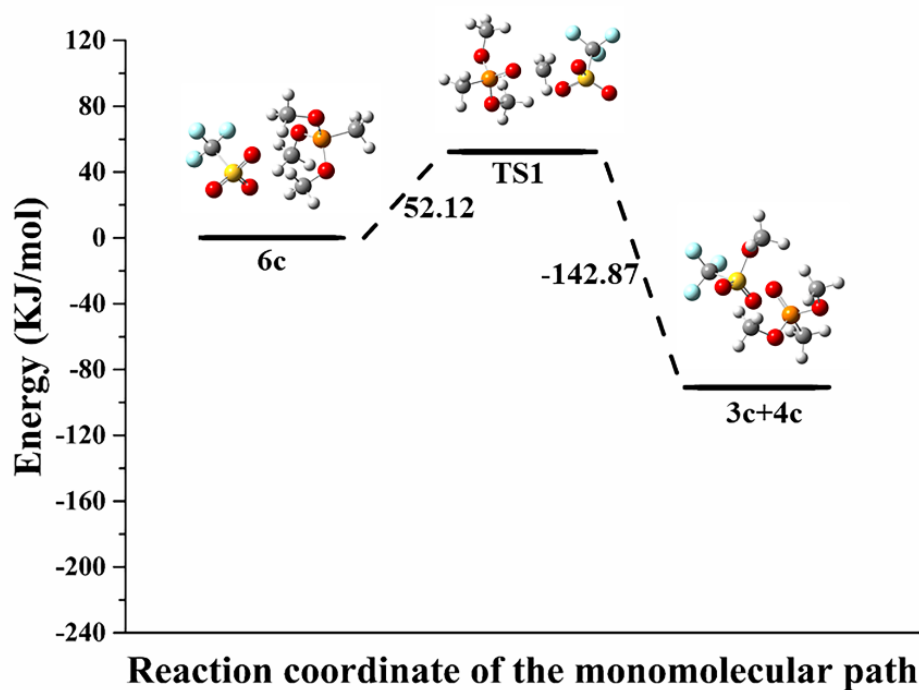


## 2-4-2. Theoretical Calculation of the Transition States

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. As shown in Figures 2-1 and 2-2, 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.

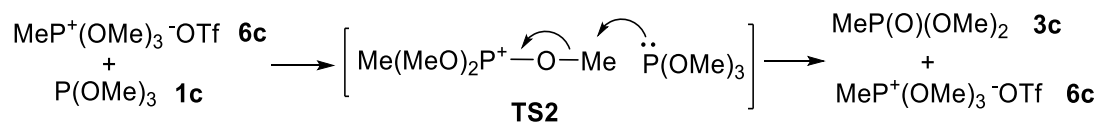
**Figure 2-1.** Theoretical Calculation of the monomolecular transition state

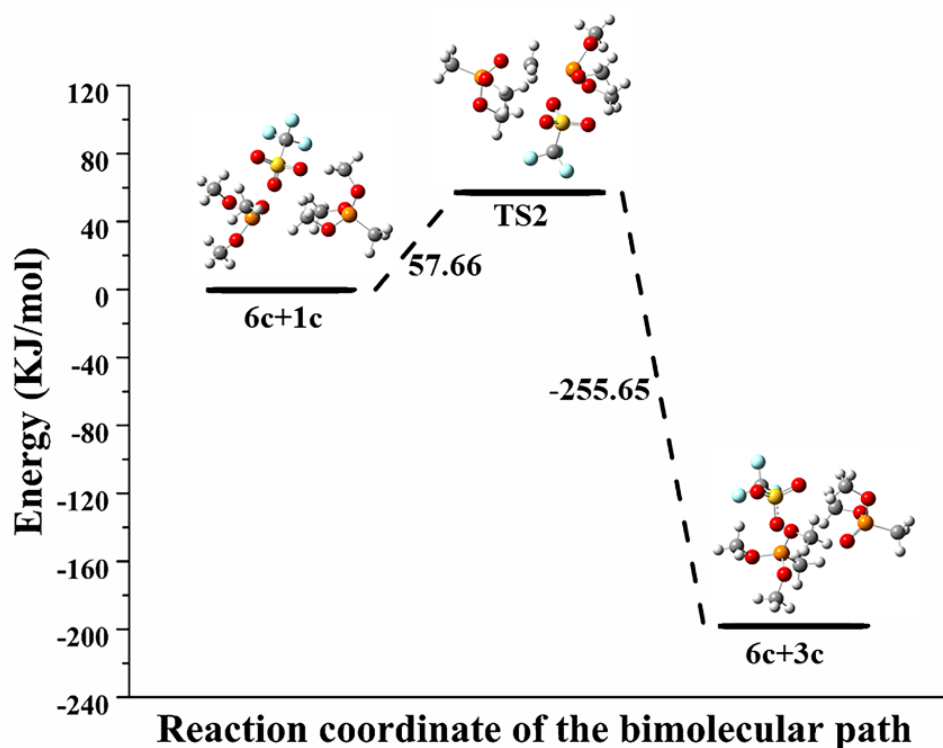




**Ball-and-stick representations.** Atoms: red: oxygen; blue: fluorine; white: hydrogen; light yellow: sulfur; gray: carbon; orange: phosphorus.

**Figure 2-2.** Theoretical Calculation of the bimolecular transition state





**Ball-and-stick representations.** Atoms: red: oxygen; blue: fluorine; white: hydrogen; light yellow: sulfur; gray: carbon; orange: phosphorus.

### 2-4-3. Proposed Mechanism

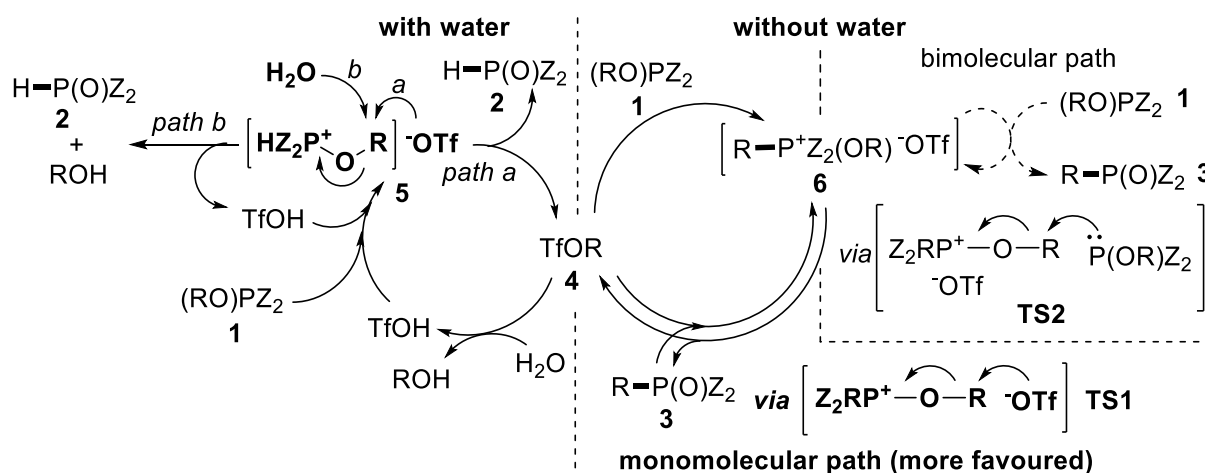
Based on above results, we proposed a possible mechanism for the Brønsted acid-catalyzed C–O cleavage reactions of P(III) esters (Scheme 2-5). Thus, TfOH may firstly protonize (RO)PZ<sub>2</sub> to give a phosphonium salt H(RO)P<sup>+</sup>Z<sub>2</sub>·<sup>−</sup>OTf (**5**).<sup>6</sup> Without water **5** may undergo C–O cleavage *via* a monomolecular S<sub>N</sub>2-type attack of TfO<sup>−</sup> at the R group of **5** to give HP(O)Z<sub>2</sub> (**2**) and TfOR.<sup>6a-b</sup> 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<sup>−</sup> is a weak nucleophile and water can very possibly compete in this process.<sup>8</sup> 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<sub>2</sub> (**2**).

In the absence of water, once a catalytic amount of TfOR (ca. 2 mol% based on the 2 mol% TfOH added)<sup>13</sup> is generated from the reaction of TfOH and (RO)PZ<sub>2</sub> (**1**), it may further react with **1** to give a new phosphonium salt R-P<sup>+</sup>Z<sub>2</sub>(OR)·<sup>−</sup>OTf (**6**). According to preceding mechanistic findings, it is more likely that TfO<sup>−</sup> will attack the RO moiety of **6** through a monomolecular S<sub>N</sub>2-type reaction to give C–O cleaved and rearranged R-P(O)Z<sub>2</sub>



(3) and regenerate TfOR.<sup>14</sup> By further reacting with the remaining (RO)PZ<sub>2</sub>, 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**.

**Scheme 2-5.** Proposed mechanism for the Brønsted acids-catalyzed C–O cleavage reactions of P(III) esters



It should also be pointed out that the above monomolecular  $S_N2$ -type mechanism may not be applied to all substrates. Clearly, for phosphites bearing an PhO group (Table 2-4, entries 7-9), the  $sp^2$  Ph group cannot undergo  $S_N2$ -type reactions with either TfO<sup>-</sup> or water nucleophiles. Alternatively, the Ph–O bond may cleave first to give the product and a Ph<sup>+</sup>. For the same reason, (PhO)PZ<sub>2</sub> cannot attack the Ph of TfOPh *via*  $S_N2$ -type process to give the corresponding phosphonium salt. Hence, P(OPh)<sub>3</sub> (**1i**) could not afford the target product (Table 2-4, entry 9) and the reactions of **1g–1h** selectively occurred at the MeO moiety to give **3g–3h** (Table 2-4, entries 7-8).

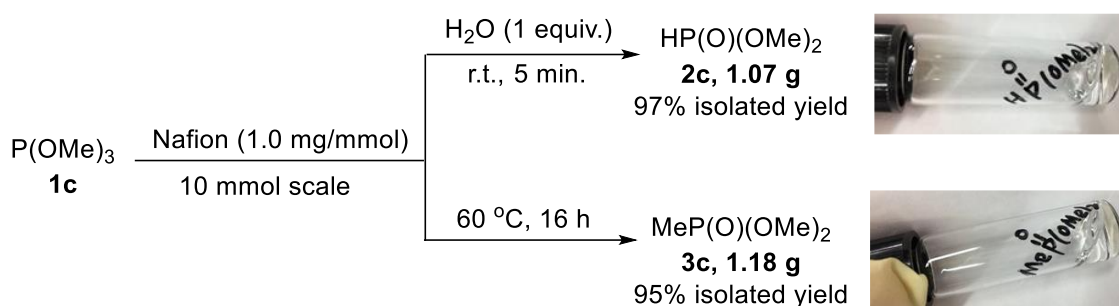
## 2-5. The Recoverable and Reusable Solid Nafion as the Catalyst

### 2-5-1. Gram Scale Reactions

Synthetic usefulness of the current method is also apparent. As shown in Scheme 2-6, we observed that solid acid Nafion<sup>15</sup> could effectively catalyze the conversion of P(OMe)<sub>3</sub> **1c** to HP(O)(OMe)<sub>2</sub> **2c** or MeP(O)(OMe)<sub>2</sub> **3c**, in almost quantitative yields, respectively. In the presence of water, a trace amount of Nafion catalyst rapidly catalyzed the hydrolysis of **1c** to **2c** at room temperature in a 10 mmol scale reaction.

After the reaction, a simple filtration removing the solid catalyst Nafion followed by evaporation of the solution under vacuum could give highly pure dimethyl phosphonate **2c** in almost quantitative yield. Similarly, in the absence of water, the reaction is very efficient for the transformation of **1c** to give the corresponding dimethyl methylphosphonate **3c** in 95% isolated yield after removing the solid catalyst by simple filtration.

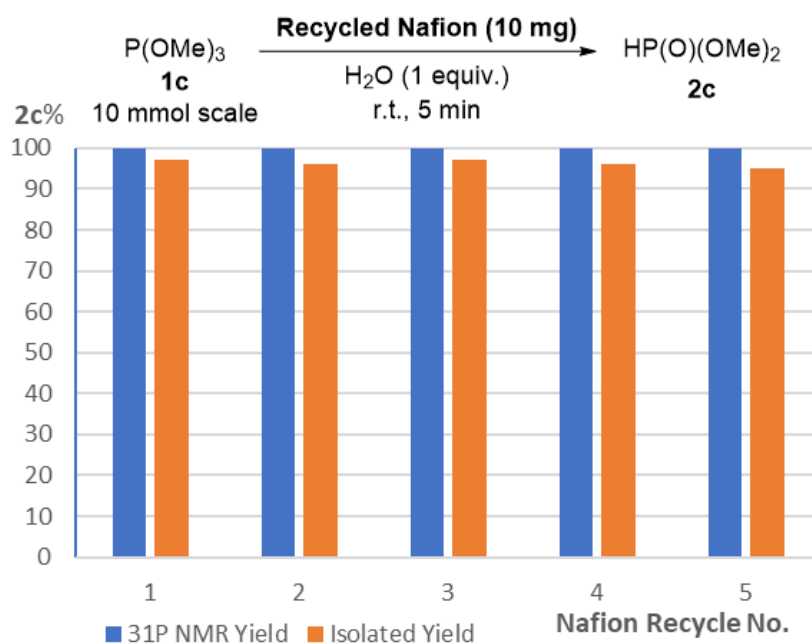
**Scheme 2-6.** Gram Scale reactions using the recoverable and reusable solid Nafion as the catalyst



## 2-5-2. Recycled Experiments

In addition, the solid Nafion catalyst can be easily recovered and reused in new reactions without losing its catalytic activity at all. As shown in Figure 2-3, the 10 mg Nafion used in the above catalytic hydrolysis of **1c** to **2c** could be recovered by simple filtration and reused for at least five cycles, all giving 95-97% isolated yields of **2c**. Even in the fifth cycle, there's no sign for Nafion to lose its activity as 100% NMR yield of **2c** was still observed and gave 95% isolated yield.

**Figure 2-3.** Recovery and reuse of solid Nafion catalyst in 10 mmol reactions



## 2-6. 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 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. 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. The solid acid Nafion is also a very active catalyst for the reactions, as it can be readily used in large scale reactions, recovered and reused for at least five cycles without losing any catalytic activity. All these revealed the method's potential utility in industrial manufacturing. Mechanistic studies showed that the reaction perhaps takes place via a monomolecular mechanism.

## 2-7. Experimental Section

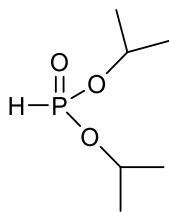
### 2-7-1. General Information

Unless otherwise noted, small scale reactions with water were carried out in NMR tubes under air atmosphere and solvent-free condition; reactions without water were carried out in oven-dried Schlenk tubes

under N<sub>2</sub> atmosphere and solvent-free condition. Dry solvents were obtained according to standard procedures. Unless otherwise noted, all reagents were purchased and used as received. Trivalent phosphorus compounds were either purchased (from TCI if commercially available) or prepared from the corresponding alcohols and phosphorus (III) chloride according to the literature procedure (P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix, C. Mioskowski, *Angew. Chem. Int. Ed.* **2003**, *42*, 2389). Product **2** were mostly purified by vacuum distillation. Product **3** were purified by a preparative GPC apparatus (JAPAN ANALYTICAL INDUSTRY LC-908 with JAIGEL-1H, polystyrene-based column) using CHCl<sub>3</sub> as the eluent (smaller scale reactions). Quaternary phosphonium salt MeP<sup>+</sup>(OMe)<sub>3</sub>·OTf (**6c**) used in the control reactions was obtained in 84% isolated yield according to the literature method (K. S. Colle, E. S. Lewis, *J. Org. Chem.* **1978**, *43*, 571). Theoretical calculation of the energy barriers of the mono- and bi-molecular transition states are obtained using GAUSSIAN 09 software with pm6 semi-empirical algorithm (M. J. Frisch, G. W. Trucks, H. B. Schlegel, et al. Gaussian 09, revision B. 01; Gaussian, Inc.: Wallingford CT, 2009). <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR spectra of the products were acquired on a JEOL JNM-ECS400 (400 MHz for <sup>1</sup>H, 100 MHz for <sup>13</sup>C, and 162 MHz for <sup>31</sup>P NMR spectroscopy). Chemical shifts for <sup>1</sup>H NMR are referred to internal Me<sub>4</sub>Si (0 ppm) and reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Chemical shifts for <sup>31</sup>P NMR were relative to H<sub>3</sub>PO<sub>4</sub> (85% solution in D<sub>2</sub>O, 0 ppm).

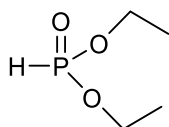
### 2-7-2. Typical procedure for Brønsted acid-catalyzed C–O cleavage of P(III) esters in the presence of H<sub>2</sub>O

To an NMR tube was added triisopropyl phosphite (**1a**) (0.52 mL, 2.3 mmol), 1 equiv. H<sub>2</sub>O (41.4 uL), trifluoromethanesulfonic acid (4 uL, 2 mol%) under air atmosphere. The tube was then sealed, slightly shaken at room temperature, and subjected to <sup>31</sup>P NMR measurement in ca. 5 min. <sup>31</sup>P NMR spectra revealed that the reaction was very fast and completed (>99% NMR yield) in the 5 min. Pure **2a** was obtained by distillation in 94% isolated yield. Except solid products HP(O)Ph<sub>2</sub> (**2k**) and HP(O)Cy<sub>2</sub> (**2p**) that were obtained by recrystallization, all other products were purified by vacuum distillation.



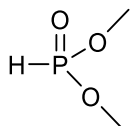
#### Diisopropyl phosphite (2a).

Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.67 (s, 0.5H), 5.95 (s, 0.5H), 4.74-4.66 (m, 2H), 1.33 (d,  $J = 2.4$  Hz, 6H), 1.32 (d,  $J = 2.4$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  70.8 (d,  $J_{\text{C-P}} = 5.4$  Hz), 24.0 (d,  $J_{\text{C-P}} = 4.0$  Hz), 23.8 (d,  $J_{\text{C-P}} = 4.5$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.92. This compound was known: H. C. Fisher, L. Prost, J.-L. Montchamp, *Eur. J. Org. Chem.* **2013**, 2013, 7973.



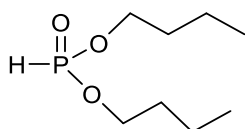
#### Diethyl phosphite (2b).

Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.63 (s, 0.5H), 5.90 (s, 0.5H), 4.14-4.06 (m, 4H), 1.32 (t,  $J = 7.0$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  61.7, 16.3.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80. This compound was known: H. C. Fisher, L. Prost, J.-L. Montchamp, *Eur. J. Org. Chem.* **2013**, 2013, 7973.



#### Dimethyl phosphite (2c).

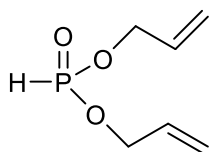
Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.60 (s, 0.5H), 5.85 (s, 0.5H), 3.74 (t,  $J = 12.0$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  52.1 (d,  $J_{\text{C-P}} = 5.7$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.1. This compound was known: H. Fakhraian, A. Mirzaei, *Org. Process Res. Dev.* **2004**, 8, 401.



#### Dibutyl phosphite (2d).

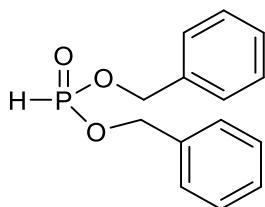
Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.66 (s, 0.5H), 5.93 (s, 0.5H), 4.06 (q,  $J = 6.8$  Hz, 4H), 1.70-1.63 (m, 4H), 1.46-1.36 (m, 4H), 0.93 (d,  $J = 7.4$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  65.6 (d,  $J_{\text{C-P}} = 5.8$  Hz), 32.5 (d,  $J_{\text{C-P}} = 6.2$  Hz), 18.8, 13.6.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.41. This compound was known: H. C.

Fisher, L. Prost, J.-L. Montchamp, *Eur. J. Org. Chem.* **2013**, 2013, 7973.



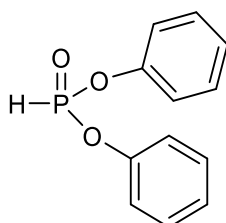
**Diallyl phosphite (2e).**

Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.76 (s, 0.5H), 6.00 (s, 0.5H), 5.98-5.89 (m, 2H), 0.93 (d,  $J = 7.4$  Hz, 2H), 0.93 (d,  $J = 7.4$  Hz, 2H), 4.59-4.55 (m, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  132.3 (d,  $J_{\text{C-P}} = 5.9$  Hz), 118.6, 66.2 (d,  $J_{\text{C-P}} = 5.4$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.26. This compound was known: P. A. Lohse, R. Felber, *Tetrahedron Lett.* **1998**, 39, 2067.



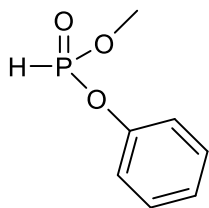
**Dibenzyl phosphite (2f).**

Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36-7.25 (m, 10H), 6.93 (d,  $J = 707.6$  Hz, 1H), 5.11-5.00 (m, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  135.7, 135.6, 128.8, 128.1, 67.4 (d,  $J_{\text{C-P}} = 5.7$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.36. This compound was known: H. C. Fisher, L. Prost, J.-L. Montchamp, *Eur. J. Org. Chem.* **2013**, 2013, 7973.



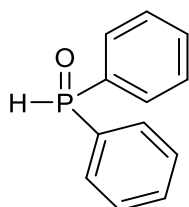
**Diphenyl phosphite (2i).**

Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.21 (s, 0.5H), 7.37-7.33 (m, 4H), 7.25-7.19 (m, 6H), 6.39 (s, 0.5H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.4 (d,  $J_{\text{C-P}} = 8.1$  Hz), 130.1, 125.9, 120.6 (d,  $J_{\text{C-P}} = 4.8$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.82. This compound was known: H. C. Fisher, L. Prost, J.-L. Montchamp, *Eur. J. Org. Chem.* **2013**, 2013, 7973.



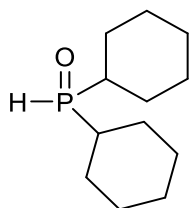
**Methoxyphenylphosphine oxide (2j).**

Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.66 (s, 0.5H), 7.25-7.19 (m, 2H), 6.90-76.85 (m, 3H), 5.89 (s, 0.5H), 3.78 (d,  $J = 11.6$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.4, 129.6, 120.2, 115.5, 52.5 (d,  $J_{\text{C-P}} = 5.7$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.1. This compound was known: E. Jablonkai, R. Henyecz, M. Milen, J. Kóti, G. Keglevich, *Tetrahedron* **2014**, 70, 8280.



**Diphenylphosphine oxide (2k).**

White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.66 (s, 0.5H), 7.72-7.66 (m, 4H), 7.57-7.53 (m, 2H), 7.50-7.46 (m, 4.5H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  132.6, 131.6 (d,  $J_{\text{C-P}} = 101.3$  Hz), 130.8 (d,  $J_{\text{C-P}} = 11.3$  Hz), 129.0 (d,  $J_{\text{C-P}} = 12.9$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.02. This compound was known: C. A. Busacca, J. C. Lorenz, N. Grinberg, N. Haddad, M. Hrapchak, B. Latli, H. Lee, P. Sabila, A. Saha, M. Sarvestani, S. Shen, R. Varsolona, X. Wei, C. H. Senanayake, *Org. Lett.* **2005**, 7, 4277.



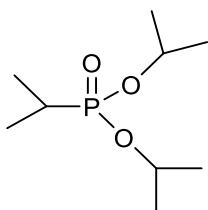
**Dicyclohexylphosphine oxide (2p).**

White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.84 (t,  $J = 2.6$  Hz, 0.5H), 5.75 (t,  $J = 2.8$  Hz, 0.5H), 1.99-1.71 (m, 12H), 1.48-1.40 (m, 4H), 1.31-1.19 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  34.9 (d,  $J_{\text{C-P}} = 64.2$  Hz), 26.2 (d,  $J_{\text{C-P}} = 25.8$  Hz), 26.2, 25.8, 25.0 (d,  $J_{\text{C-P}} = 3.0$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  50.22. This compound was known: C. A. Busacca, J. C. Lorenz, N. Grinberg, N. Haddad, M. Hrapchak, B. Latli, H. Lee, P. Sabila, A.

Saha, M. Sarvestani, S. Shen, R. Varsolona, X. Wei, C. H. Senanayake, *Org. Lett.* **2005**, 7, 4277.

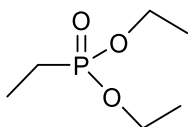
### 2-7-3. Typical procedure for Brønsted acid-catalyzed C–O cleavage of P(III) esters in the absence of H<sub>2</sub>O

To a 10 mL Schlenk tube was added triethyl phosphite (**1b**) (0.4 mL, 2.3 mmol) and trifluoromethanesulfonic acid (4 uL, 2 mol%) under N<sub>2</sub>. The tube was then heated at 60 °C for 16 h and **1b** was totally consumed. Pure **3b** was obtained by preparative GPC in 95% isolated yield.



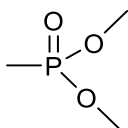
#### Diisopropyl isopropylphosphonate (**3a**).

Colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.69-4.61 (m, 2H), 1.89-1.77 (m, 1H), 1.27 (dd, *J* = 6.4 Hz, 2.0 Hz, 12H), 1.15 (d, *J* = 6.8 Hz 3H), 1.10 (d, *J* = 7.2 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 69.6 (d, *J*<sub>C-P</sub> = 7.0 Hz), 26.4 (d, *J*<sub>C-P</sub> = 143 Hz), 24.1 (d, *J*<sub>C-P</sub> = 3.2 Hz), 24.0 (d, *J*<sub>C-P</sub> = 4.6 Hz). <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>): δ 34.01. This compound was known: J. Acharya, P. D. Shakya, D. Pardasani, M. Palit, D. K. Dubey, A. K. Gupta, *J. Chem. Res.* **2005**, 2005, 194.



#### Diethyl ethylphosphonate (**3b**).

Colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.15-4.01 (m, 4H), 1.72 (dq, *J* = 18.1, 7.6 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.15 (dt, *J* = 20.0 Hz, 7.6 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 61.5 (d, *J*<sub>C-P</sub> = 6.5 Hz), 18.8 (d, *J*<sub>C-P</sub> = 141.9 Hz), 16.5 (d, *J*<sub>C-P</sub> = 5.9 Hz), 6.6 (d, *J*<sub>C-P</sub> = 6.9 Hz). <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>): δ 34.19. This compound was known: J. Acharya, P. D. Shakya, D. Pardasani, M. Palit, D. K. Dubey, A. K. Gupta, *J. Chem. Res.* **2005**, 2005, 194.

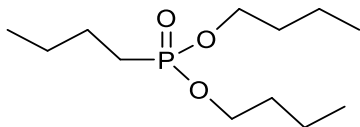


#### Dimethyl methylphosphonate (**3c**).



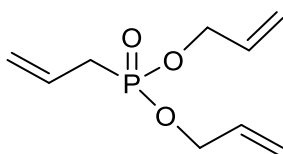
Colorless oil.  $^1\text{H}$  NMR (400 MHz  $\text{CDCl}_3$ ):  $\delta$  3.67 (d,  $J = 11.2$  Hz, 6H), 1.41 (d,  $J = 17.6$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  52.2 (d,  $J_{\text{C-P}} = 6.1$  Hz), 9.9 (d,  $J_{\text{C-P}} = 143.7$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  33.81.

This compound was known: P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix, C. Mioskowski, *Angew. Chem. Int. Ed.* **2003**, *42*, 2389. This compound was known:



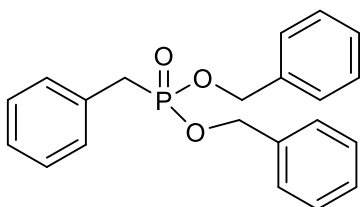
**Dibutyl butylphosphonate (3d).**

Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.95-3.86 (m, 4H), 1.66-1.41 (m, 8H), 1.34-1.25 (m, 6H), 0.85-0.78 (m, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  65.1 (d,  $J_{\text{C-P}} = 6.7$  Hz), 32.6 (d,  $J_{\text{C-P}} = 6.0$  Hz), 25.2 (d,  $J_{\text{C-P}} = 146.4$  Hz), 24.5, 23.7 (d,  $J_{\text{C-P}} = 17.2$  Hz), 18.8, 13.6, 13.5.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  33.12. This compound was known: T. Wolf, T. Steinbach, F. R. Wurm, *Macromolecules* **2015**, *48*, 3853.



**Diallyl allylphosphonate (3e).**

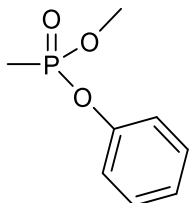
Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.90-5.80 (m, 2H), 5.79-5.67 (m, 1H), 5.30-5.25 (m, 2H), 5.18-5.11 (m, 4H), 4.49-4.44 (m, 4H), 2.62-2.54 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  133.0 (d,  $J_{\text{C-P}} = 6.0$  Hz), 127.2 (d,  $J_{\text{C-P}} = 11.3$  Hz), 120.3 (d,  $J_{\text{C-P}} = 14.5$  Hz), 117.9, 66.4 (d,  $J_{\text{C-P}} = 6.5$  Hz), 31.9 (d,  $J_{\text{C-P}} = 138.8$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.45. This compound was known: X. Lu, J. Zhu, *J. Organometallic Chemistry* **1986**, *304*, 239.



**Dibenzyl benzylphosphonate (3f).**

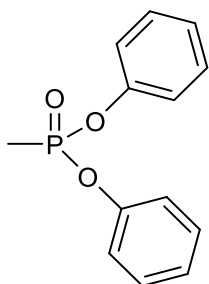
Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33-7.24 (m, 15H), 4.92 (d,  $J = 8.4$  Hz, 4H), 3.19 (d,  $J = 21.6$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  136.4 (d,  $J_{\text{C-P}} = 5.9$  Hz), 131.3 (d,  $J_{\text{C-P}} = 9.3$  Hz), 130.0 (d,  $J_{\text{C-P}} = 6.6$  Hz).

Hz), 128.7 (d,  $J_{C-P}$  = 3.0 Hz), 128.6, 128.4, 128.0, 127.1 (d,  $J_{C-P}$  = 3.6 Hz), 67.7 (d,  $J_{C-P}$  = 6.6 Hz), 34.2 (d,  $J_{C-P}$  = 137.1 Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.13. This compound was known: L. Gavara, C. Petit, J.-L. Montchamp, *Tetrahedron Lett.* **2012**, 53, 5000.



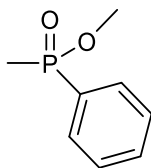
**Methyl phenyl methylphosphonate (3g).**

Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.29-7.25 (m, 2H), 7.15-7.08 (m, 3H), 3.73 (dd,  $J$  = 11.2 Hz, 1.2 Hz, 2H), 1.55 (dd,  $J$  = 17.6 Hz, 1.2 Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.5 (d,  $J_{C-P}$  = 8.0 Hz), 129.9, 125.1, 120.5 (d,  $J_{C-P}$  = 4.1 Hz), 52.7 (d,  $J_{C-P}$  = 6.6 Hz), 10.8 (d,  $J_{C-P}$  = 144.2 Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.37. This compound was known: M. Fañanás-Mastral, B. L. Feringa, *J. Am. Chem. Soc.* **2014**, 136, 9894.



**Diphenyl methylphosphonate (3h).**

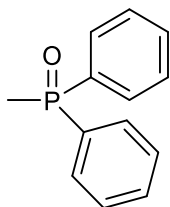
Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33-7.29 (m, 4H), 7.20-7.14 (m, 6H), 1.78 (d,  $J$  = 17.6 Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.4 (d,  $J_{C-P}$  = 8.3 Hz), 129.9, 125.3, 120.6 (d,  $J_{C-P}$  = 4.5 Hz), 11.6 (d,  $J_{C-P}$  = 144.3 Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.55. This compound was known: L. Gavara, C. Petit, J.-L. Montchamp, *Tetrahedron Lett.* **2012**, 53, 5000.



**Methyl methylphenylphosphinate (3j).**

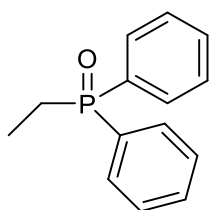
Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78-7.73 (m, 2H), 7.55-7.44 (m, 3H), 3.58 (d,  $J$  = 11.2 Hz, 3H),

1.64 (d,  $J = 14.8$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  132.4 (d,  $J_{\text{C-P}} = 2.5$  Hz), 131.4 (d,  $J_{\text{C-P}} = 9.9$  Hz), 131.1 (d,  $J_{\text{C-P}} = 125.9$  Hz), 128.8 (d,  $J_{\text{C-P}} = 12.6$  Hz), 51.1 (d,  $J_{\text{C-P}} = 6.1$  Hz), 15.6 (d,  $J_{\text{C-P}} = 102.5$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  44.43. This compound was known: P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix, C. Mioskowski, *Angew. Chem. Int. Ed.* **2003**, 42, 2389.



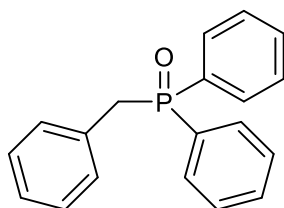
### Methyldiphenylphosphine oxide (3k).

White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.74-7.69 (m, 4H), 7.51-7.43 (m, 6H), 2.01 (d,  $J = 13.2$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  134.1 (d,  $J_{\text{C-P}} = 100.9$  Hz), 131.8 (d,  $J_{\text{C-P}} = 2.6$  Hz), 130.6 (d,  $J_{\text{C-P}} = 9.7$  Hz), 128.7 (d,  $J_{\text{C-P}} = 12.0$  Hz), 16.6 (d,  $J_{\text{C-P}} = 73.4$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.57. This compound was known: P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix, C. Mioskowski, *Angew. Chem. Int. Ed.* **2003**, 42, 2389.



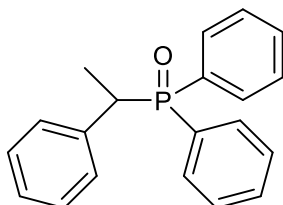
### Ethyldiphenylphosphine oxide (3l).

White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.73-7.68 (m, 4H), 7.50-7.41 (m, 6H), 2.29-2.21 (m, 2H), 1.21-1.13 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  134.1 (d,  $J_{\text{C-P}} = 100.9$  Hz), 131.8 (d,  $J_{\text{C-P}} = 2.6$  Hz), 130.6 (d,  $J_{\text{C-P}} = 9.7$  Hz), 128.7 (d,  $J_{\text{C-P}} = 12.0$  Hz), 16.6 (d,  $J_{\text{C-P}} = 73.4$  Hz), 5.7 (d,  $J_{\text{C-P}} = 5.0$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  34.73. This compound was known: P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix, C. Mioskowski, *Angew. Chem. Int. Ed.* **2003**, 42, 2389.



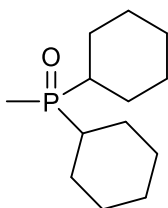
### Benzoyldiphenylphosphine oxide (3n).

White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.70-7.65 (m, 4H), 7.49-7.38 (m, 6H), 7.16-7.08 (m, 5H), 3.63 (d,  $J = 14.0$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  132.4 (d,  $J_{\text{C-P}} = 98.9$  Hz), 131.9 (d,  $J_{\text{C-P}} = 2.2$  Hz), 131.3 (d,  $J_{\text{C-P}} = 9.2$  Hz), 130.2 (d,  $J_{\text{C-P}} = 5.1$  Hz), 128.6, 128.5, 128.5 (d,  $J_{\text{C-P}} = 1.9$  Hz), 126.9 (d,  $J_{\text{C-P}} = 2.6$  Hz), 38.2 (d,  $J_{\text{C-P}} = 66.2$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.78. This compound was known: P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix, C. Mioskowski, *Angew. Chem. Int. Ed.* **2003**, 42, 2389.



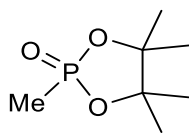
**Diphenyl(1-phenylethyl)phosphine oxide (3o).**

White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.88-7.87 (m, 2H), 7.50-7.40 (m, 5H), 7.32-7.14 (m, 8H), 3.61-3.56 (m, 1H), 1.55 (dq,  $J = 4.0$  Hz, 16.0 Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  138.0 (d,  $J_{\text{C-P}} = 5.3$  Hz), 132.5 (d,  $J_{\text{C-P}} = 14.4$  Hz), 131.8 (d,  $J_{\text{C-P}} = 2.3$  Hz), 131.5 (d,  $J_{\text{C-P}} = 8.5$  Hz), 131.2 (d,  $J_{\text{C-P}} = 8.6$  Hz), 129.3 (d,  $J_{\text{C-P}} = 5.2$  Hz), 128.8 (d,  $J_{\text{C-P}} = 11.1$  Hz), 128.3, 128.1 (d,  $J_{\text{C-P}} = 11.4$  Hz), 127.0, 41.0 (d,  $J_{\text{C-P}} = 66.9$  Hz), 15.5.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  34.21. This compound was known: P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix, C. Mioskowski, *Angew. Chem. Int. Ed.* **2003**, 42, 2389.



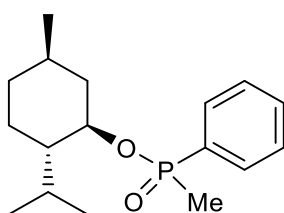
**Dicyclohexylmethylphosphine oxide (3p).**

White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.10-1.95 (m, 3H), 1.83-1.62 (m, 10H), 1.41-1.19 (m, 12H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  35.9 (d,  $J_{\text{C-P}} = 66.5$  Hz), 26.6 (d,  $J_{\text{C-P}} = 10.5$  Hz), 26.4 (d,  $J_{\text{C-P}} = 9.7$  Hz), 26.0, 25.8 (d,  $J_{\text{C-P}} = 1.5$  Hz), 24.9 (d,  $J_{\text{C-P}} = 3.0$  Hz), 8.6 (d,  $J_{\text{C-P}} = 62.0$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  51.32. This compound was known: E. Korzeniowska, A. E. Koziół, E. Łastawiecka, A. Flis, M. Stankevič, *Tetrahedron* **2017**, 73, 5153.



**2,4,4,5,5-pentamethyl-1,3,2-dioxaphosphole 2-oxide (3q).**

White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.61 (d,  $J = 17.6$  Hz, 3H), 1.38 (d,  $J = 52.0$  Hz, 12H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  88.2, 24.7 (d,  $J_{\text{C-P}} = 3.4$  Hz), 23.9 (d,  $J_{\text{C-P}} = 5.2$  Hz), 13.5 (d,  $J_{\text{C-P}} = 135.9$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  42.28. This compound was known: H. Gonçalves, J. P. Majoral, *Phosphorus, Sulfur Silicon Relat. Elem.* **1978**, 4, 343.

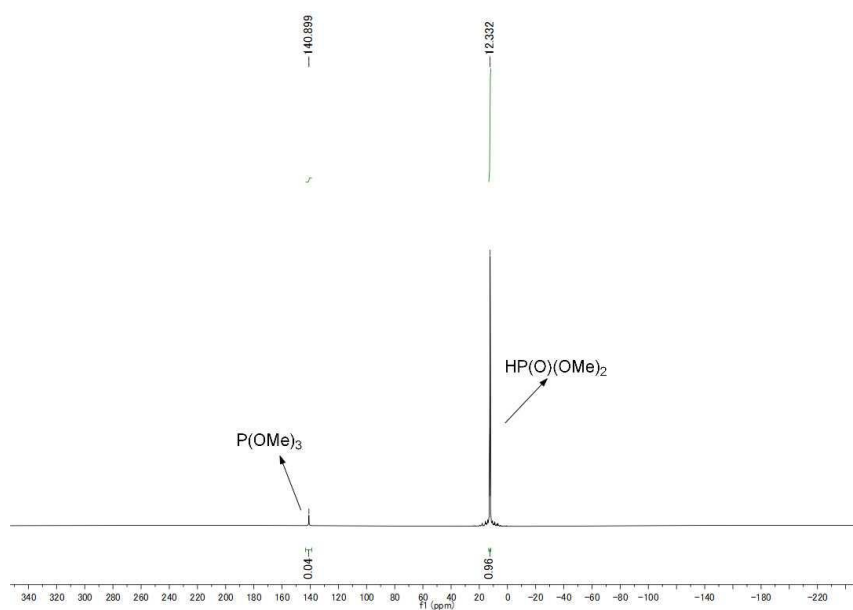


**Menthyl methylphenylphosphinate (3r).**

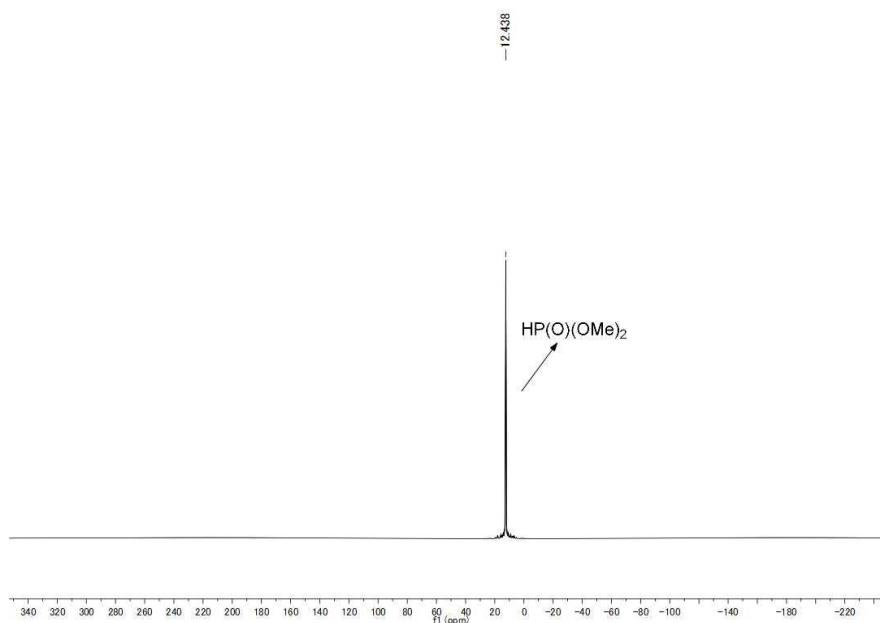
White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.81-7.76 (m, 4H), 7.53-7.49 (m, 2H), 7.46-7.42 (m, 4H), 4.30-3.90 (m, 2H), 2.2.-2.16 (m, 1H), 1.92-1.87 (m, 1H), 1.70-1.58 (m, 10H), 1.38-1.23 (m, 6H), 1.02-0.74 (m, 22H), 0.30 (d,  $J = 6.8$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  134.0 (d,  $J_{\text{C-P}} = 128.6$  Hz), 132.5 (d,  $J_{\text{C-P}} = 127.3$  Hz), 132.0 (d,  $J_{\text{C-P}} = 2.5$  Hz), 131.9 (d,  $J_{\text{C-P}} = 2.2$  Hz), 131.2 (d,  $J_{\text{C-P}} = 9.9$  Hz), 130.9 (d,  $J_{\text{C-P}} = 10.2$  Hz), 128.5 (d,  $J_{\text{C-P}} = 12.6$  Hz), 76.5 (d,  $J_{\text{C-P}} = 7.2$  Hz), 48.8 (d,  $J_{\text{C-P}} = 6.4$  Hz), 43.9, 43.3, 34.2, 31.6, 31.5, 25.9, 25.5, 23.1, 22.8, 22.0, 21.9, 21.2, 21.1, 17.1 (d,  $J_{\text{C-P}} = 3.7$  Hz), 16.1 (d,  $J_{\text{C-P}} = 2.4$  Hz), 15.9, 15.2.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  41.22, 40.56. This compound was known: W. Dabkowski, A. Ozarek, S. Olejniczak, M. Cypriak, J. Chojnowski, J. Michalski, *Chem. Eur. J.* **2009**, 15, 1747.

**2-7-4. Detailed procedure for a fast and simple way to remove  $\text{P}(\text{OMe})_3$  (1c) contaminated in  $\text{HP}(\text{O})(\text{OMe})_2$  (2c) using TfOH as the catalyst**

To a NMR tube was added dimethyl phosphite **2c** (0.78 mL, 8.46 mmol) and trimethyl phosphite **1c** (50  $\mu\text{L}$ , 0.42 mmol, 5 mol%) under air and subjected to  $^{31}\text{P}$  NMR measurement. Then, TfOH (0.75  $\mu\text{L}$ , 0.17 mmol, 2 mol%) and  $\text{H}_2\text{O}$  (7.6  $\mu\text{L}$ , 0.42 mmol, 5 mol%) were added to the NMR tube. The tube was slightly shaken at room temperature and subjected to  $^{31}\text{P}$  NMR measurement in ca. 5 min.  $^{31}\text{P}$  NMR spectra revealed that the reaction completed quantitatively in the 5 min. Pure **2c** was observed in 100%  $^{31}\text{P}$  NMR yield.



**$^{31}\text{P}$  NMR before the reaction [ $\text{HP}(\text{O})(\text{OMe})_2 + 5 \text{ mol\% } \text{P}(\text{MeO})_3$ ]**



**$^{31}\text{P}$  NMR after the reaction [ $\text{HP}(\text{O})(\text{OMe})_2$  only]**

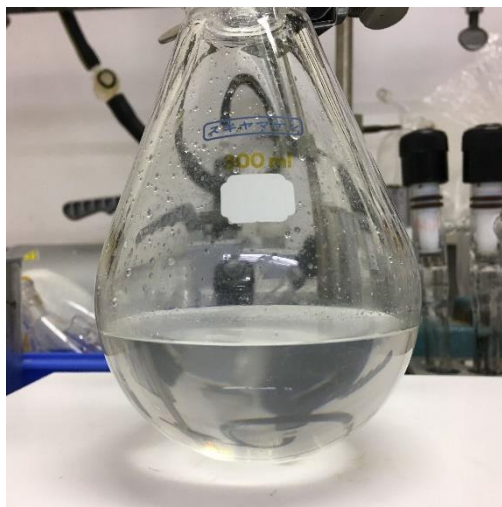
## **2-7-5. Detailed procedure for 100 gram scale reaction of TfOH-catalyzed C–O cleavage of $\text{P}(\text{OMe})_3$ in the presence of $\text{H}_2\text{O}$**

Trimethyl phosphite **1c** (100 g, 806 mmol), TfOH (71  $\mu\text{L}$ , 0.1 mol%), and  $\text{H}_2\text{O}$  (14.5 mL, 1 equiv.) was mixed by stirring in a 300 mL round-bottomed flask at 0 °C under air, slowly warmed to room temperature, and then stirred at room temperature for more 30 min.  $^{31}\text{P}$  NMR analysis of the reaction mixture revealed that the reaction completed in the 30 min. to afford dimethyl phosphite **2c** in almost quantitative yield (>99% NMR

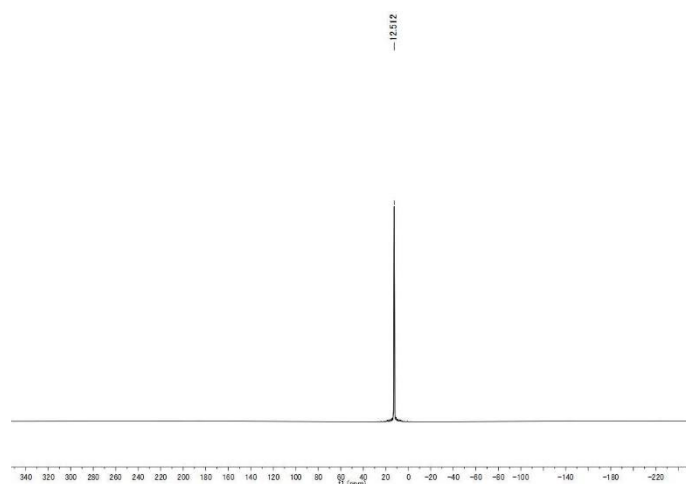
yield). Pure **2c** was obtained by usual vacuum distillation in 93% yield (82.4 g, see the  $^{31}\text{P}$  NMR spectra below for purity).



**Before the reaction**



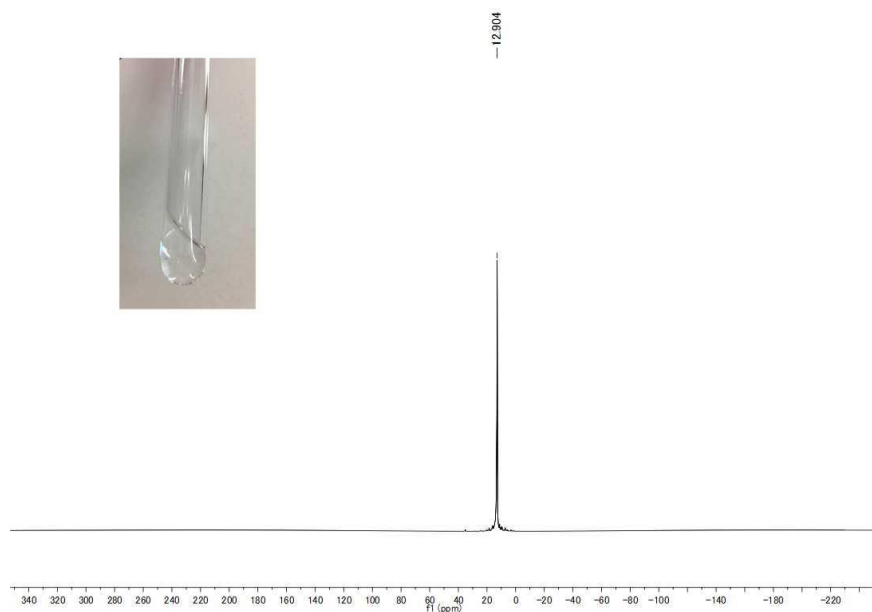
**After the reaction**



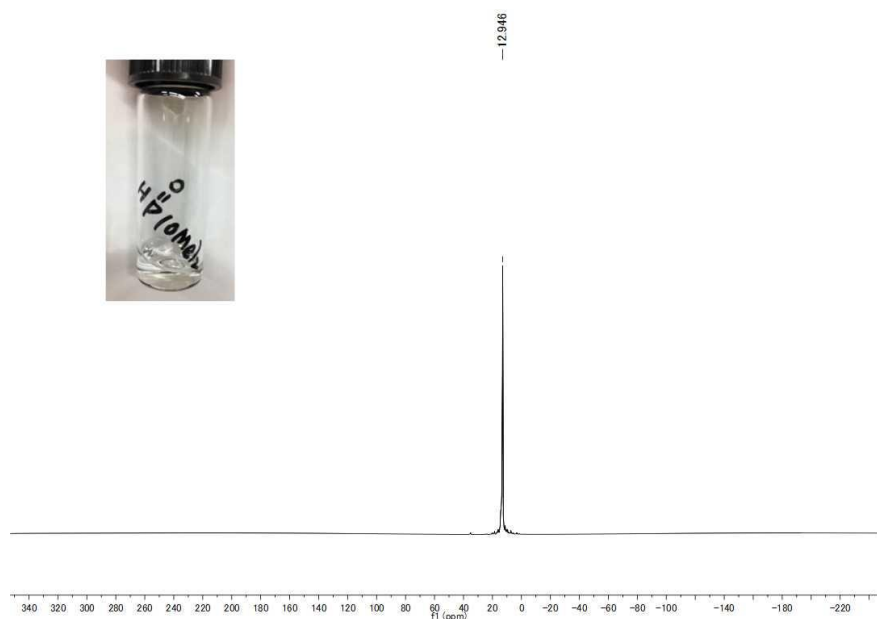
**$^{31}\text{P}$  NMR of purified  $\text{HP}(\text{O})(\text{OMe})_2$  (**2c**)**

#### **2-7-6. Detailed procedure for 10 mmol scale synthesis of $\text{HP}(\text{O})(\text{OMe})_2$ (**2c**) using Nafion as the catalyst**

To a 10 mL Schlenk tube was added Nafion (10 mg, 1.0 mg/mmol), trimethyl phosphite **1c** (1.18 mL, 10 mmol), and  $\text{H}_2\text{O}$  (180  $\mu\text{L}$ , 1 equiv.) under air. The tube was then sealed, slightly shaken at room temperature, and subjected to  $^{31}\text{P}$  NMR measurement in ca. 5 min.  $^{31}\text{P}$  NMR spectra revealed that the reaction completed quantitatively in the 5 min. Pure **2c** was obtained by filtration in 97% isolated yield.



$^{31}\text{P}$  NMR (2c) before filtration



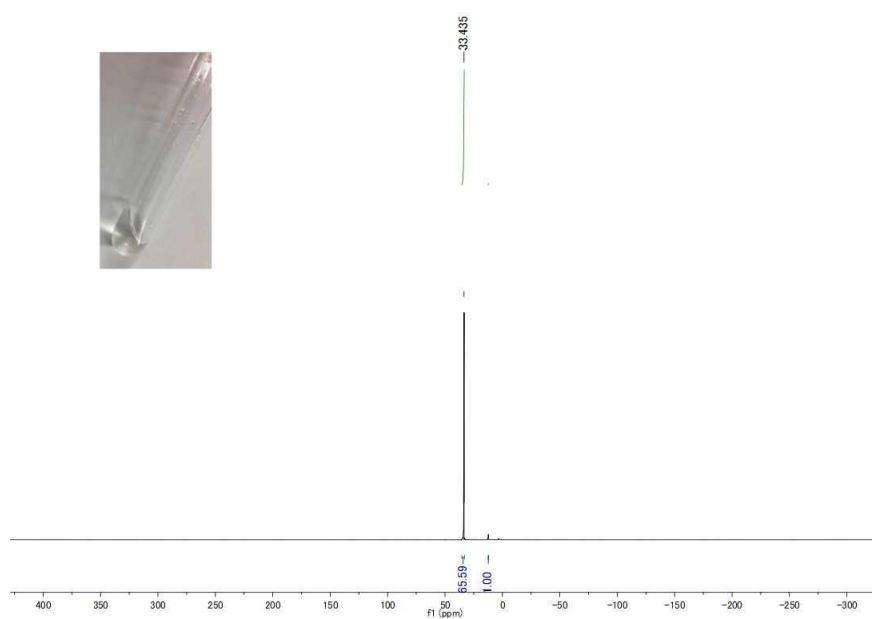
$^{31}\text{P}$  NMR (2c) after filtration

#### 2-7-7. Detailed procedure for 10 mmol scale synthesis of $\text{MeP}(\text{O})(\text{OMe})_2$ (**3c**) using Nafion as the catalyst

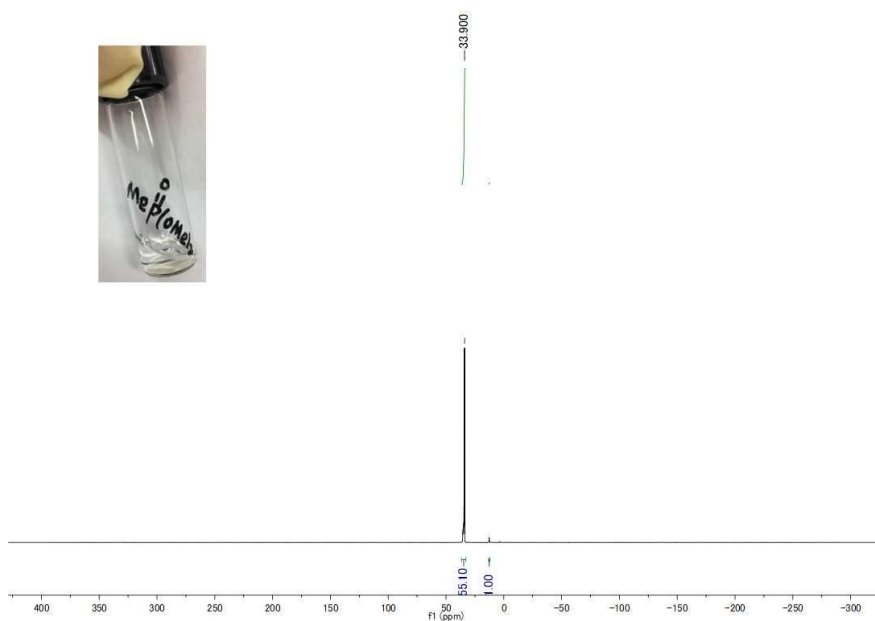
To a 10 mL Schlenk tube was added Nafion (10 mg, 1.0 mg/mmol) and trimethyl phosphite **1c** (1.18 mL, 10 mmol) under  $\text{N}_2$ . The tube was then heated at 60 °C for 16 h and **1c** was totally consumed.  $^{31}\text{P}$  NMR spectra revealed that the reaction completed almost quantitatively. Pure **3c** was obtained by filtration in 95% isolated



yield.



**$^{31}\text{P}$  NMR (3c) before filtration**



**$^{31}\text{P}$  NMR (3c) after filtration**

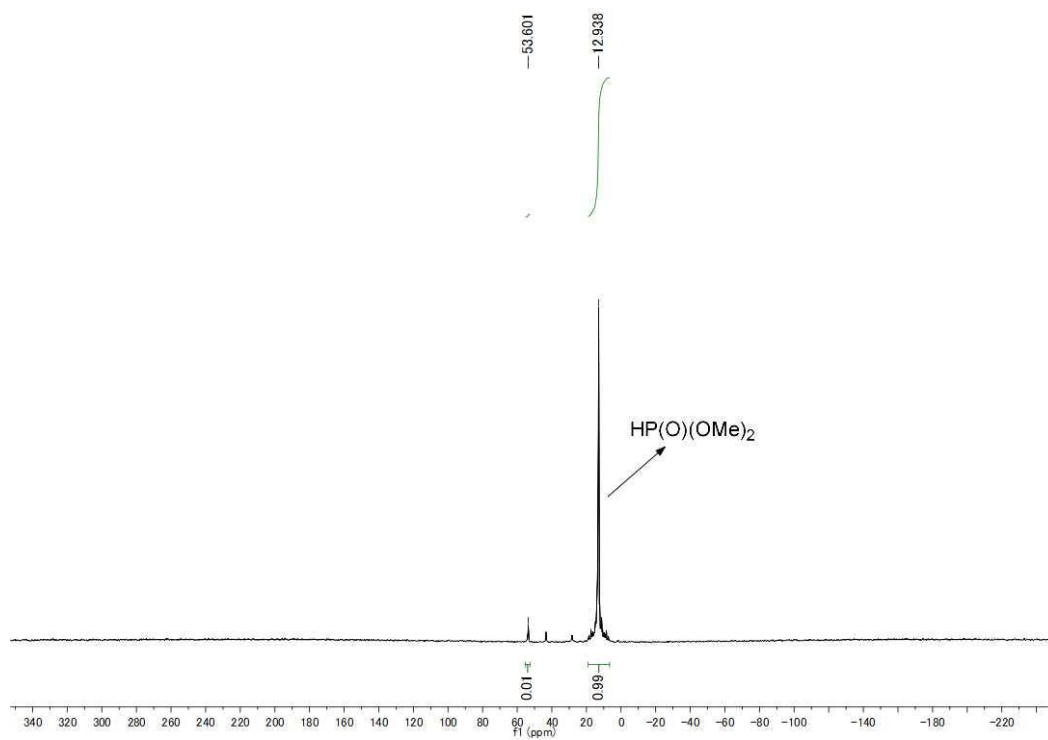
## **2-7-8. Detailed procedure for the solid Nafion catalyst recovered and reused in 10 mmol scale synthesis of $\text{HP}(\text{O})(\text{OMe})_2$ (2c)**

To a 10 mL Schlenk tube was added Nafion (10 mg, 1.0 mg/mmol), trimethyl phosphite **1c** (1.18 mL, 10 mmol), and  $\text{H}_2\text{O}$  (180  $\mu\text{L}$ , 1 equiv.) under air. The tube was then sealed, slightly shaken at room temperature,

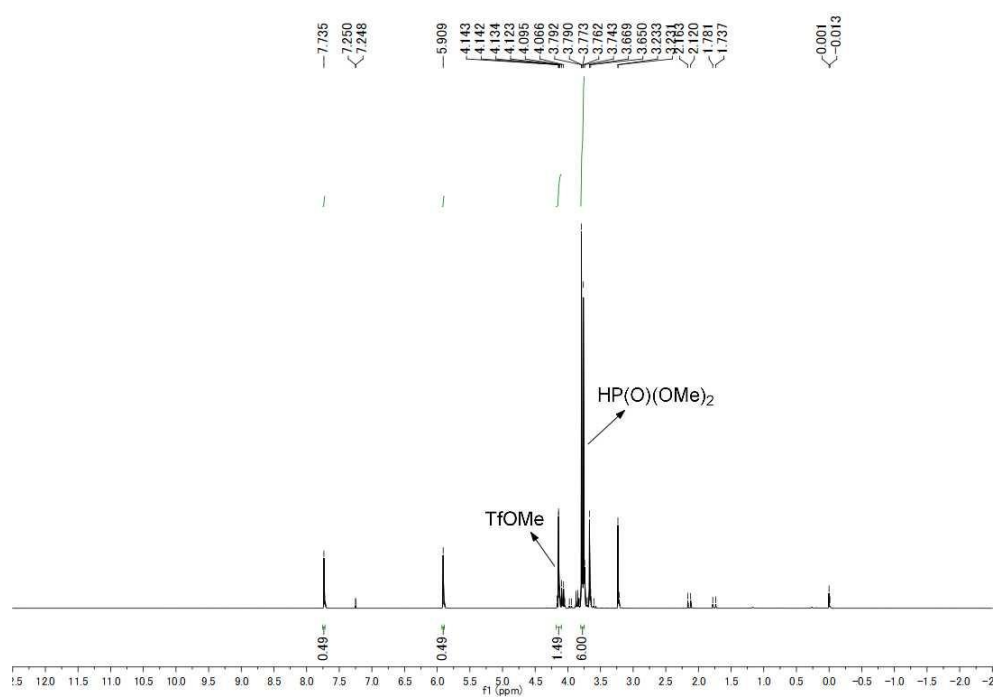
and subjected to  $^{31}\text{P}$  NMR measurement in ca. 5 min.  $^{31}\text{P}$  NMR spectra revealed that the reaction completed quantitatively in the 5 min. Pure **2c** was obtained by filtration in 97% isolated yield. Then the solid Nafion catalyst was separated by filtration, washed with hexane four times, and dried under vacuum at room temperature for a few minutes. The recovered solid Nafion catalyst was used for the subsequent run by adding fresh substrate. The recovered solid Nafion catalyst was used for four subsequent runs, and the results of these experiments are summarized in Figure 1. As shown in Figure 1, the 10 mg Nafion used in the above catalytic hydrolysis of **1c** to **2c** could be recovered by simple filtration and reused for at least five cycles, all giving 95-97% isolated yields of **2c**. Even in the fifth cycle, there's no sign for Nafion to lose its activity as 100% NMR yield of **2c** was still observed and gave 95% isolated yield.

#### **2-7-9. Stoichiometric reaction of P(OMe)<sub>3</sub> (**1a**) and TfOH (eq. 2-3)**

**Detailed Procedure:** To an NMR tube cooled at 0 °C were successively added  $\text{CDCl}_3$  (0.5 mL), trifluoromethanesulfonic acid (37.5  $\mu\text{L}$ , 0.424 mmol), and trimethyl phosphite (**1a**) (50  $\mu\text{L}$ , 1 equiv.) dropwise under  $\text{N}_2$ . The tube was then slowly warmed to room temperature and remained for 2 h.  $^{31}\text{P}$  NMR spectra of the reaction mixture revealed that the reaction completed to afford dimethyl phosphite **2c** in almost quantitative yield (see the  $^{31}\text{P}$  NMR spectra below).  $^1\text{H}$  NMR spectra of the reaction mixture revealed that methyl trifluoromethanesulfonate (**4c**) was generated in ca. 50% yield (see the  $^1\text{H}$  NMR spectra below).



$^{31}\text{P}$  NMR



$^1\text{H}$  NMR

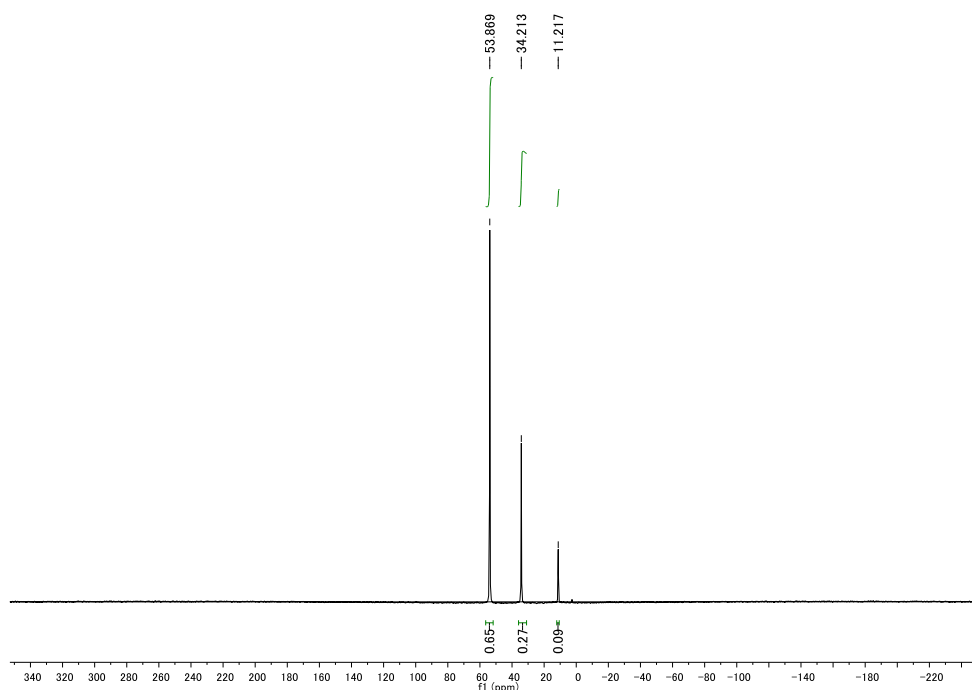
**Results and Discussion:** This reaction confirmed that stoichiometric reaction of  $\text{P(OMe)}_3$  (**1a**) and  $\text{TfOH}$

can afford a quantitative yield of dimethyl phosphite **2c**, which very possibly proceeded via the formation of phosphonium salt  $\text{HP}^+(\text{OMe})_3\cdot\text{OTf}$  (**5c**) by protonation of **1c** with TfOH followed by an intramolecular  $\text{S}_{\text{N}}2$  attack of  $\text{TfO}^-$  at a Me group of **5c**.

## 2-7-10. Stoichiometric reaction of $\text{P}(\text{OMe})_3$ (**1a**) and TfOMe (eq. 2-4)

**Detailed Procedure for Entry 1** (according to the literature method: K. S. Colle, E. S. Lewis, *J. Org. Chem.* **1978**, 43, 571): To a 10 mL Schlenk tube containing a stirring bar cooled at 0 °C were successively added  $\text{Et}_2\text{O}$  (2 mL), methyl trifluoromethanesulfonate (**4c**) (186  $\mu\text{L}$ , 1.7 mmol), and trimethyl phosphite (**1a**) (0.2 mL, 1 equiv.) dropwise under  $\text{N}_2$ . The tube was then slowly warmed to room temperature and stirred for 1 h. A white solid precipitated from the reaction mixture, which was collected by filtration and washed twice with  $\text{Et}_2\text{O}$  under  $\text{N}_2$  (in glove box). The white solid,  $\text{MeP}^+(\text{OMe})_3\cdot\text{OTf}$  (**6c**), was obtained in 84% isolated yield (412.3 mg) after vacuum drying.

**Detailed Procedure for Entry 2:** To an NMR tube cooled at 0 °C were successively added  $\text{CDCl}_3$  (2 mL), methyl trifluoromethanesulfonate (**4c**) (186  $\mu\text{L}$ , 1.7 mmol), and trimethyl phosphite (**1a**) (0.2 mL, 1 equiv.) dropwise under  $\text{N}_2$ . The tube was then slowly warmed to room temperature and stirred for 1 h.  $^{31}\text{P}$  NMR spectra revealed that the reaction completed to afford **6c** in 65% NMR yield (45% isolated yield) and **3c** in 27% NMR yield, respectively.

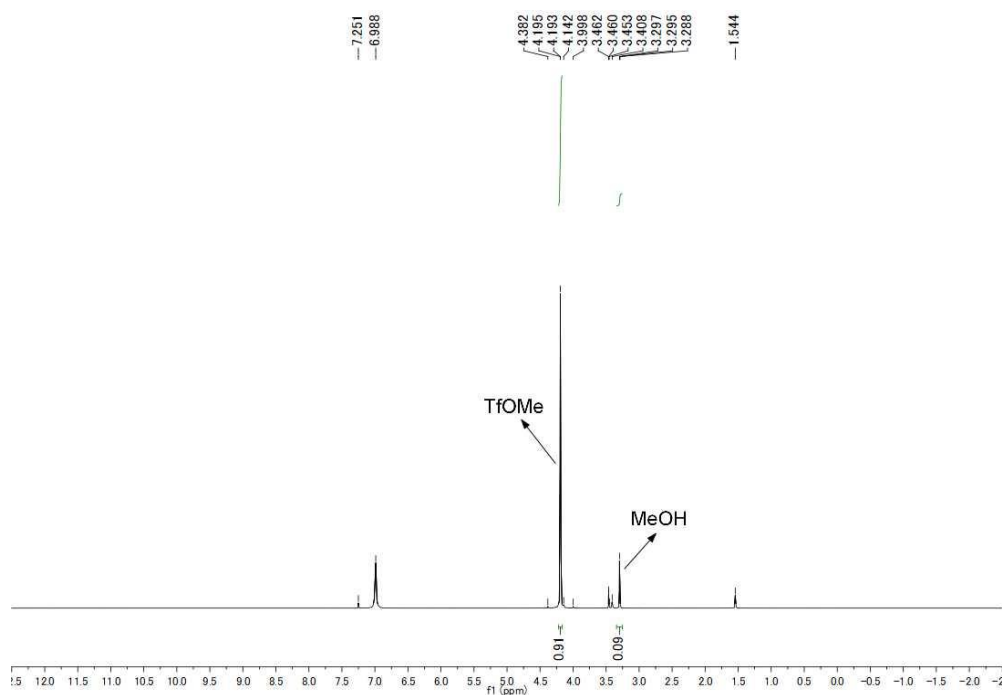


## <sup>31</sup>P NMR of the reaction mixture of entry 2

**Results and Discussion:** According to the literature method (K. S. Colle, E. S. Lewis, *J. Org. Chem.* **1978**, 43, 571), Et<sub>2</sub>O is not a good solvent for MeP<sup>+</sup>(OMe)<sub>3</sub>·OTf (**6c**), so it can easily precipitated from the Et<sub>2</sub>O mixture of **4c** and **1c** and be obtained in a good 84% isolated yield by filtration (entry 1). In contrast, CDCl<sub>3</sub> is a better solvent (see also eqs. 2-9 and 2-10, in which solvation of **6c** in CDCl<sub>3</sub> quickly leads to its conversion to **3c**). Most likely for the same reason, the generated **6c** in the CDCl<sub>3</sub> mixture of **4c** and **1c** also quickly converted to **3c**. Subsequently, only a much lower yield of **6c** was observed with observation of a considerable amount of **3c** (entry 2). This result suggests that the conversion of **6c** to **3c** may be very fast.

### 2-7-11. Hydrolysis of TfOMe (**4c**) (eq. 2-5)

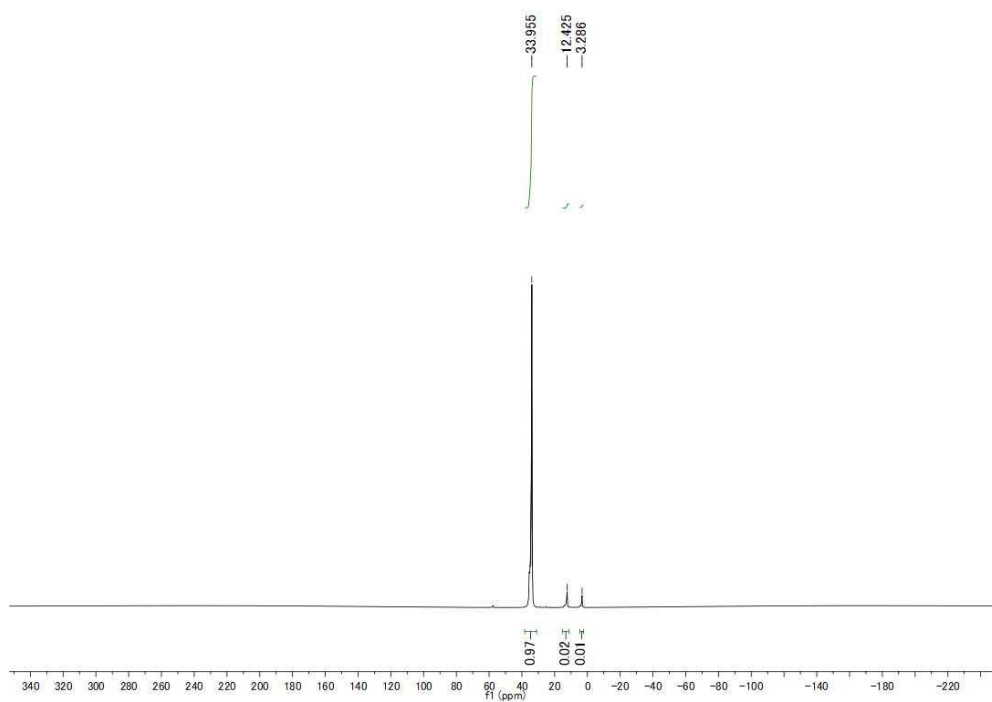
**Detailed Procedure:** To an NMR tube was added CDCl<sub>3</sub> (0.5 mL), methyl trifluoromethanesulfonate (**4c**) (46.4 uL, 0.424 mmol), and H<sub>2</sub>O (7.7uL, 1 equiv.) under N<sub>2</sub>. After standing at room temperature overnight, the tube was subjected to <sup>1</sup>H NMR measurement, revealing that **4c** was partially hydrolyzed to MeOH. This result confirmed the hydrolysis of TfOMe (**4c**) in the presence of water.



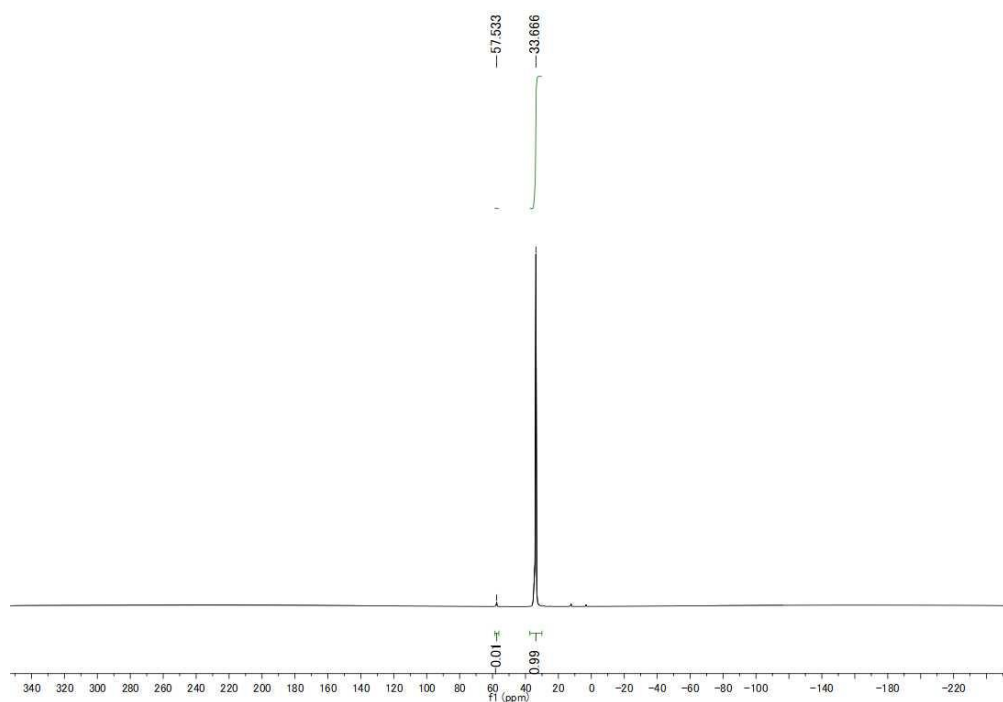
<sup>1</sup>H NMR

**2-7-12. TfOMe (4c) or MeP<sup>+</sup>(OMe)<sub>3</sub>·OTf (6c) catalyzed transformation of P(OMe)<sub>3</sub> (1c) (eq. 2-6)**

**Detailed Procedures:** To an NMR tube was added trimethyl phosphite (**1a**) (0.4 mL, 3.4 mmol) and methyl trifluoromethanesulfonate (**4c**) (7.4  $\mu$ L, 2 mol%) or phosphonium salt MeP<sup>+</sup>(OMe)<sub>3</sub>·OTf (**6c**) (19.7 mg, 2 mol%) under N<sub>2</sub>. The mixtures were then heated to 60 °C for 16 h. <sup>31</sup>P NMR spectra revealed that the reactions were complete. The methyl trifluoromethanesulfonate (**4c**) catalyzed reaction afforded **3c** in 97% yield. The phosphonium salt MeP<sup>+</sup>(OMe)<sub>3</sub>·OTf (**6c**) catalyzed reaction afforded **3c** in 99% yield.



**<sup>31</sup>P NMR of 4c-catalyzed reaction**

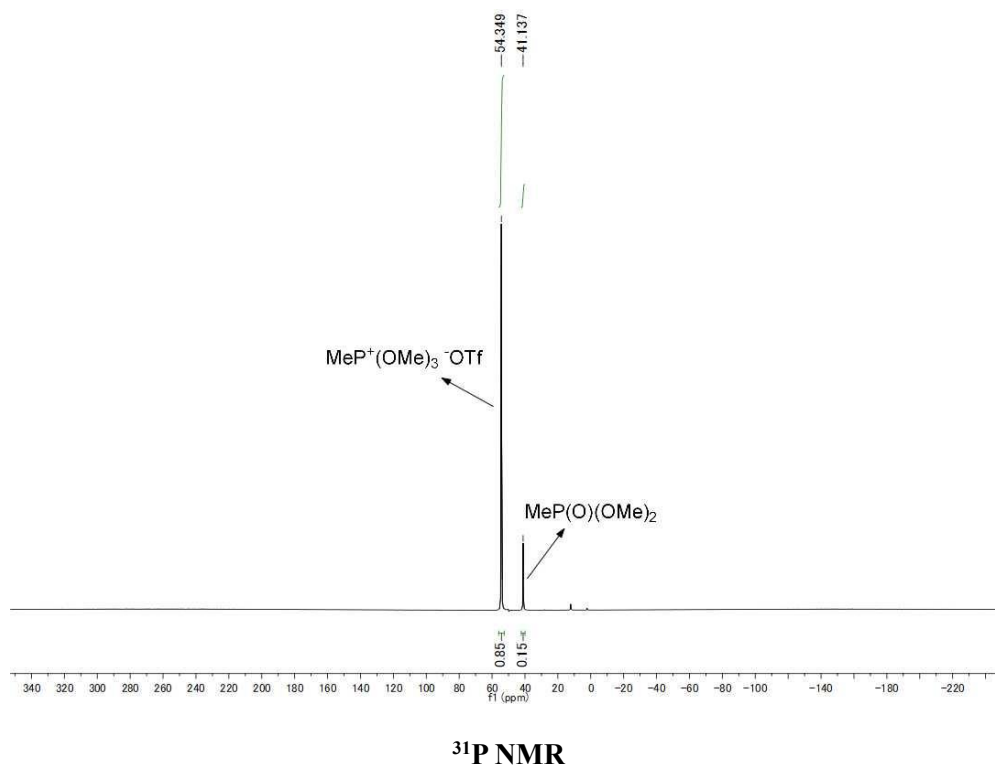


**$^{31}\text{P}$  NMR of **6c**-catalyzed reaction**

**Results and Discussion:** The above results indicated that **4c** and **6c** could catalyze the model reaction effectively to give almost quantitative yields of **3c**, suggesting an interesting mechanism that may involve TfOR (**4**) and  $\text{RP}^+(\text{OR})_3 \cdot \text{OTf}$  (**6**) as the active catalysts/intermediates.

### 2-7-13. Stoichiometric reaction of $\text{MeP}(\text{O})(\text{OMe})_2$ (**3c**) and TfOMe (**4c**) (eq. 2-7)

**Detailed procedure:** To an NMR tube was added dimethyl methylphosphonate (**3c**) (0.37 mL, 3.4 mmol) and methyl trifluoromethanesulfonate (**4c**) (0.37 mL, 1 equiv.) under  $\text{N}_2$  at room temperature. The tube was then sealed, slightly shaken, and subjected to  $^{31}\text{P}$  NMR measurement in ca. 30 min.  $^{31}\text{P}$  NMR spectra revealed that **6c** was obtained in 85% yield.

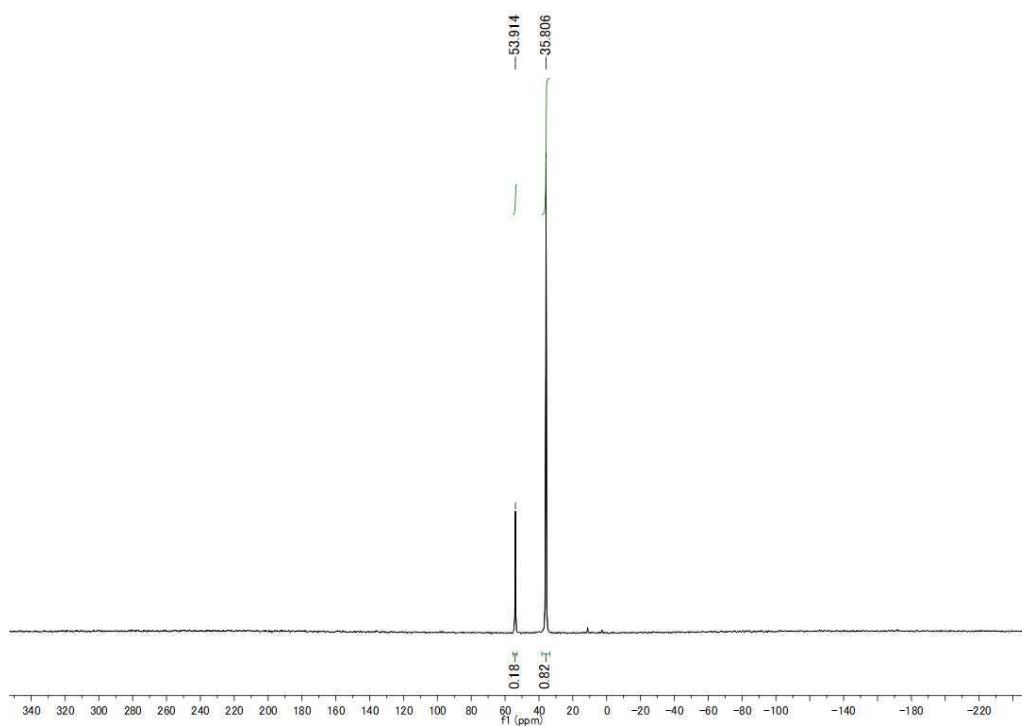


**Results and Discussion:** The above result indicated that product **3c** could also react with **4c** fastly to give a high yield of **6c**. This is consistent with the equilibrium between **3**, **4** and **6** as documented from the literature.

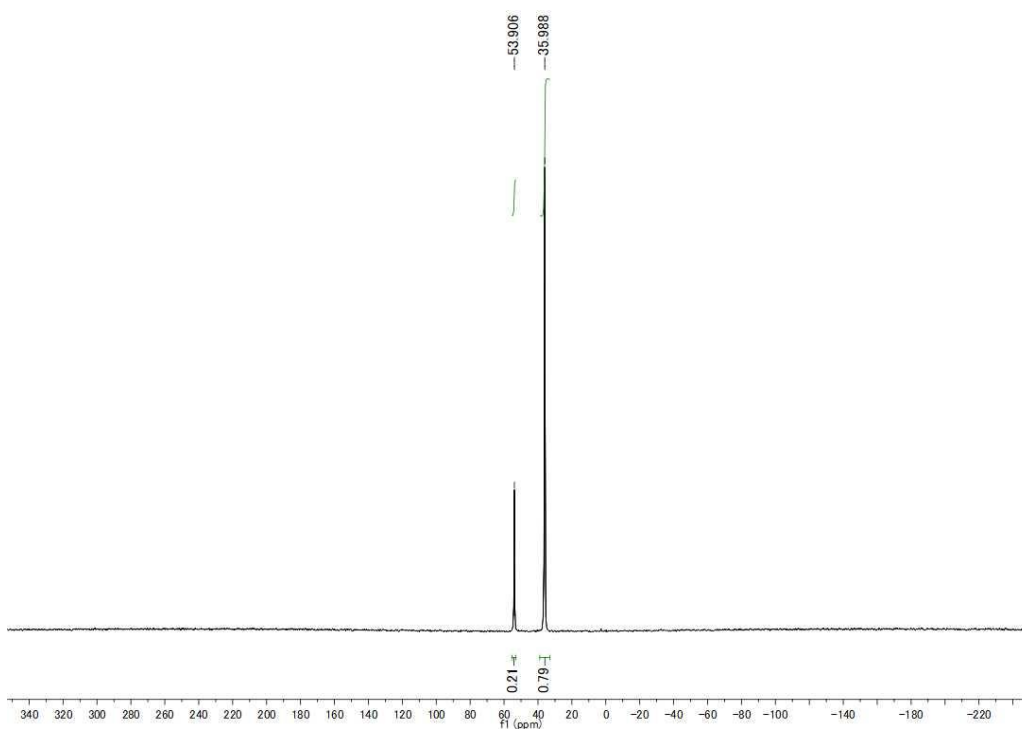
#### 2-7-14. Conversion of pure $\text{MeP}^+(\text{OMe})_3 \cdot \text{OTf}$ (**6c**) to product **3c** (eq. 2-9)

**Detailed Procedure for Entry 1 at 60 °C:** The phosphonium salt  $\text{MeP}^+(\text{OMe})_3 \cdot \text{OTf}$  (**6c**) (121.8 mg, 0.42 mmol) solved in  $\text{CDCl}_3$  (0.5 mL) sealed in an NMR tube under  $\text{N}_2$  was heated at 60 °C and measured by  $^{31}\text{P}$  NMR at 6 h, 19 h, and 24 h, respectively.  $^{31}\text{P}$  NMR spectra revealed that **3c** was formed in 82%, 79%, and 76% yields, respectively.

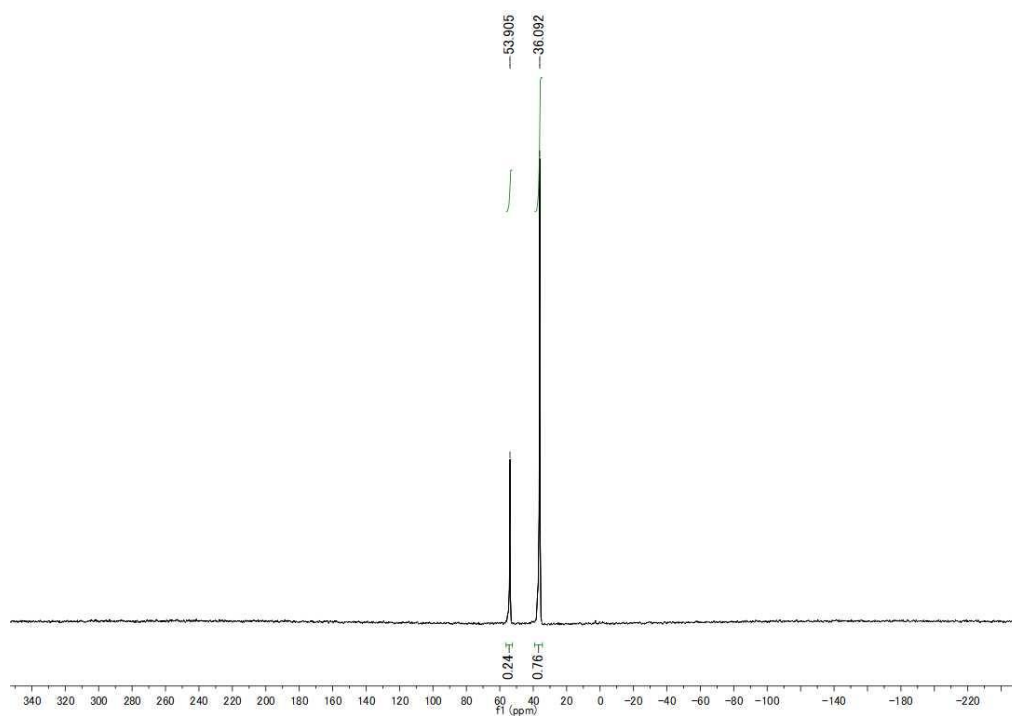




$^{31}\text{P}$  NMR (60 °C, 6 h)

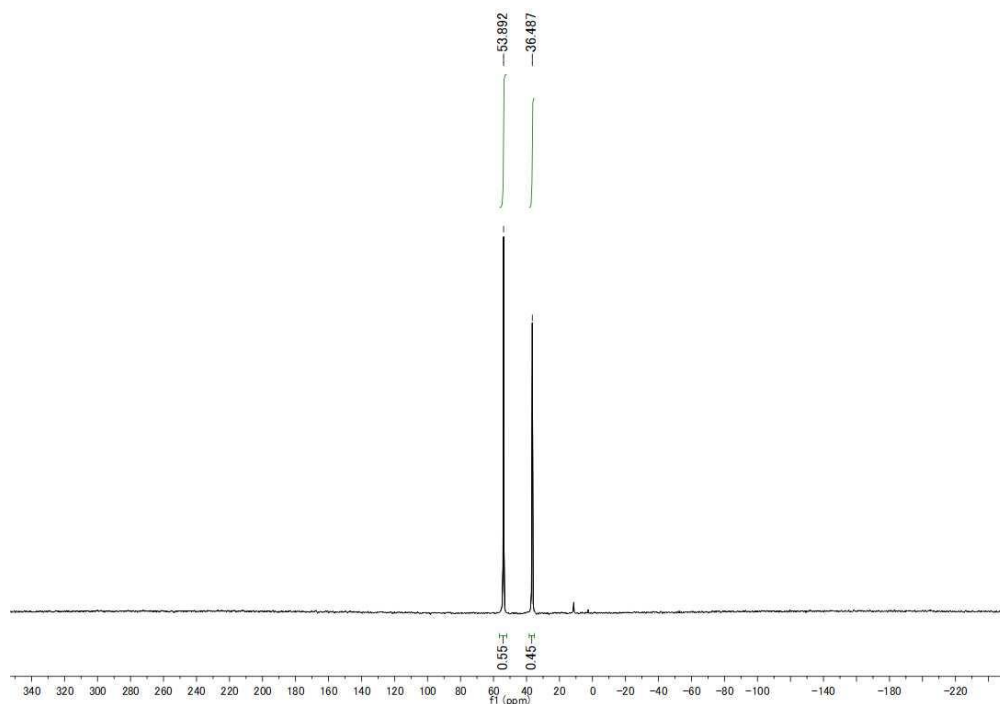


$^{31}\text{P}$  NMR (60 °C, 19 h)

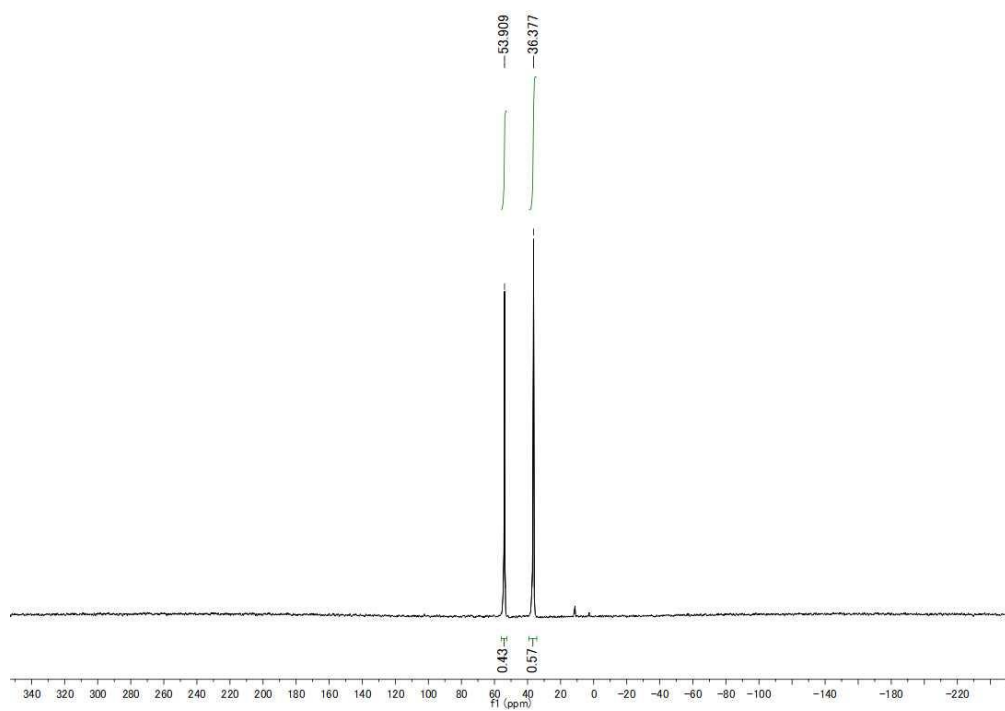


$^{31}\text{P}$  NMR (60 °C, 24 h)

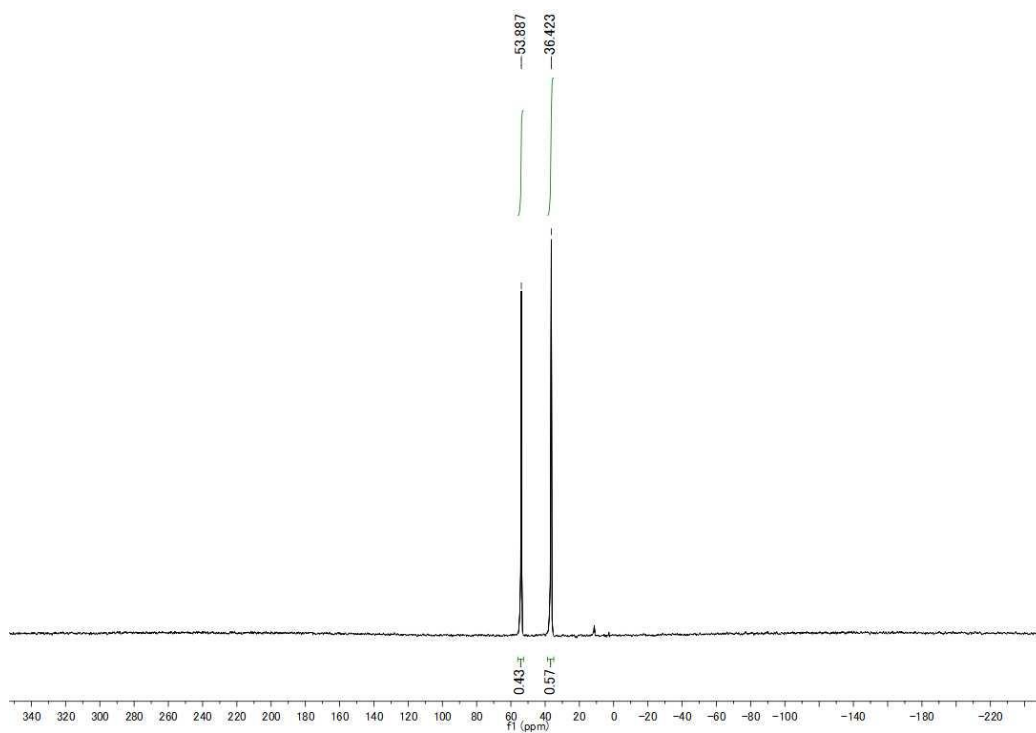
**Detailed Procedure for Entry 2 at Room Temperature:** The phosphonium salt  $\text{MeP}^+(\text{OMe})_3 \cdot \text{OTf}$  (**6c**) (121.8 mg, 0.42 mmol) solved in  $\text{CDCl}_3$  (0.5 mL) sealed in an NMR tube under  $\text{N}_2$  was slightly shaken at room temperature and measured by  $^{31}\text{P}$  NMR at 6 h, 19 h, and 24 h, respectively.  $^{31}\text{P}$  NMR spectra revealed that **3c** was formed in 45%, 57%, and 57% yields, respectively.



**$^{31}\text{P}$  NMR (r.t., 6 h)**



**$^{31}\text{P}$  NMR (r.t., 19 h)**

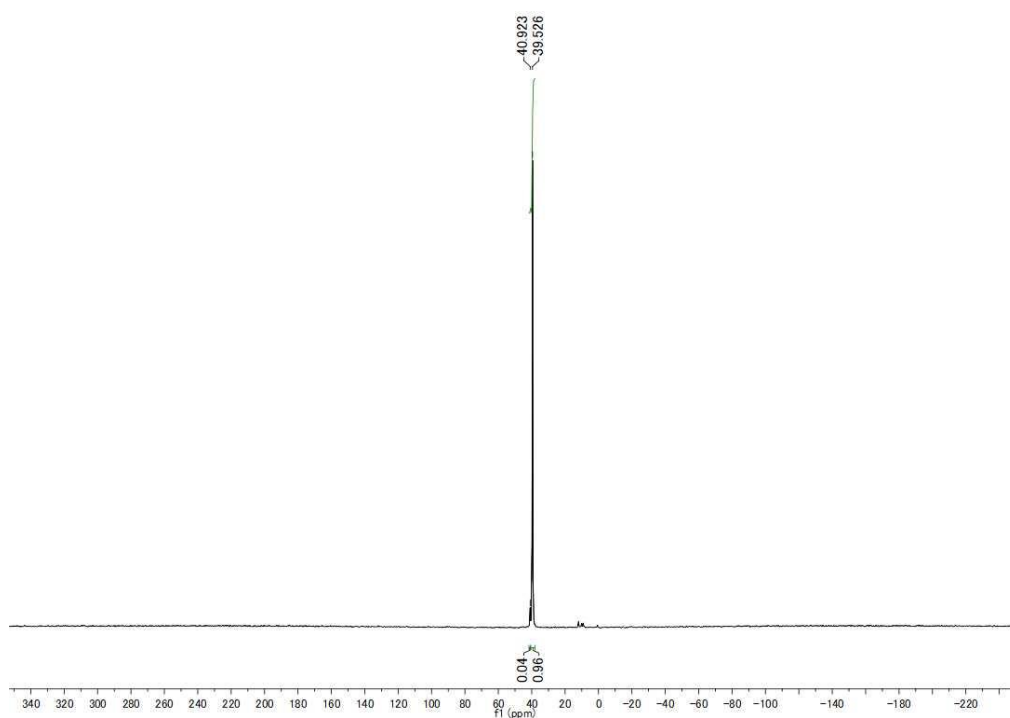


**$^{31}\text{P}$  NMR (r.t., 24 h)**

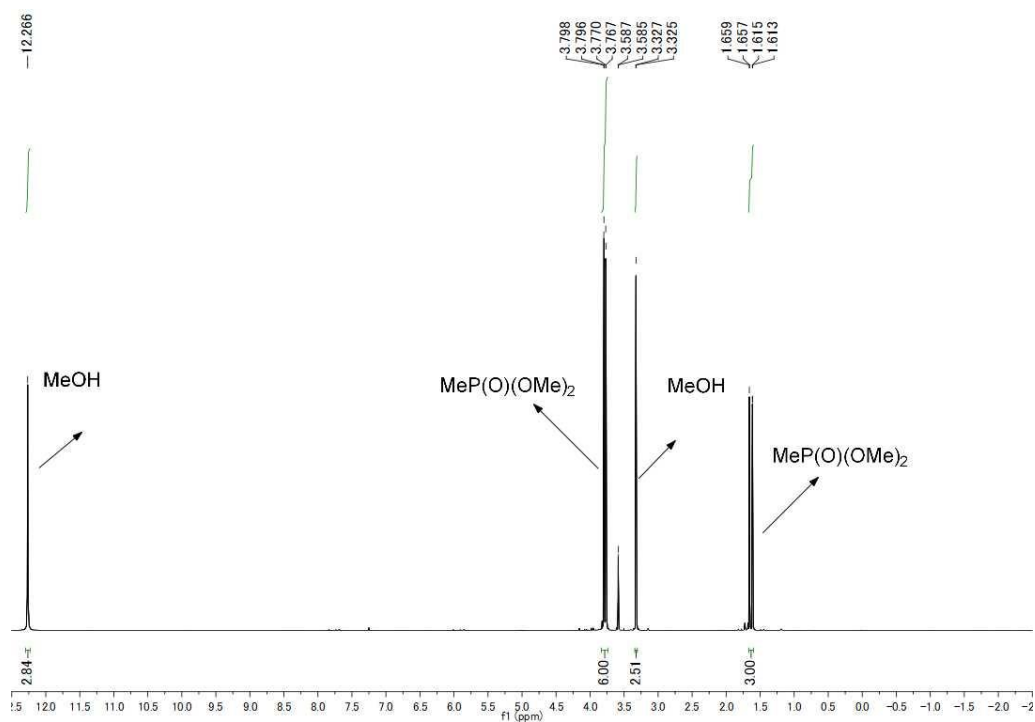
**Results and Discussion:** The above results indicated that conversion of **6c** to **3c** is rather fast under the standard conditions (60 °C) or even at room temperature. The close yields of **3c** at 19 and 24 h (79% and 76% yields at 60 °C; 57% and 57% yields at room temperature) also revealed that both reactions have reached the equilibrium between **3c**, **4c**, and **6c** at 60 °C or at room temperature. Since **1c** did not present in the reaction, the reaction possibly proceeded via a monomolecular mechanism (the textbook mechanism suggested by Arbuzov) involving the S<sub>N</sub>2 attack of TfO<sup>-</sup> at a Me group of **6c** (similar to the one shown in eq. 2-3).

### 2-7-15. Conversion of pure MeP<sup>+</sup>(OMe)<sub>3</sub>·OTf (**6c**) to product **3c** in the presence of H<sub>2</sub>O (eq. 2-10)

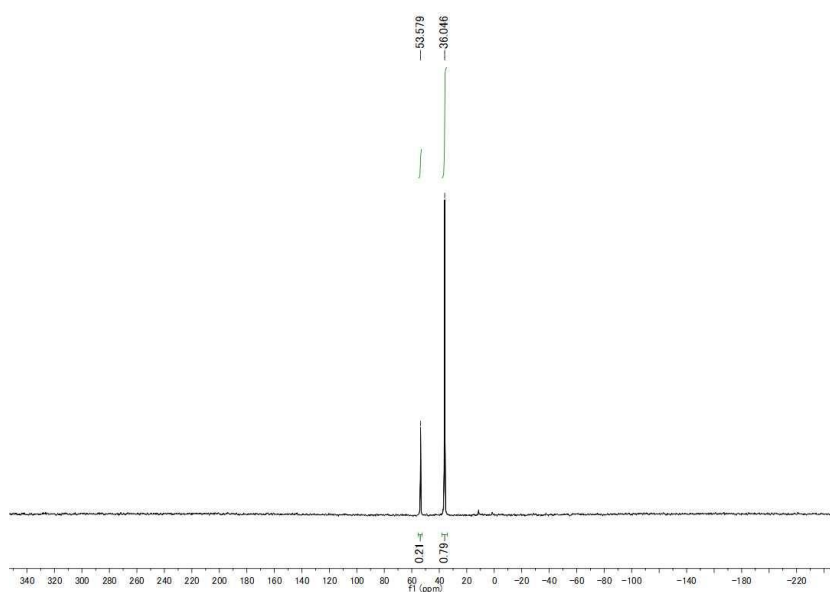
**Detailed Procedure for Entry 1 at 60 °C:** The mixture of phosphonium salt MeP<sup>+</sup>(OMe)<sub>3</sub>·OTf (**6c**) (121.8 mg, 0.42 mmol) and H<sub>2</sub>O (8.3 uL, 1.1 equiv.) in CDCl<sub>3</sub> (0.5 mL) in an NMR tube sealed under N<sub>2</sub> was heated at 60 °C for 6 h. <sup>31</sup>P NMR spectra of the reaction mixture revealed that the reaction completed to afford **3c** in 96% yield (see the <sup>31</sup>P NMR spectra below). <sup>1</sup>H NMR spectra revealed that MeOH (TfOH altogether) was also generated.

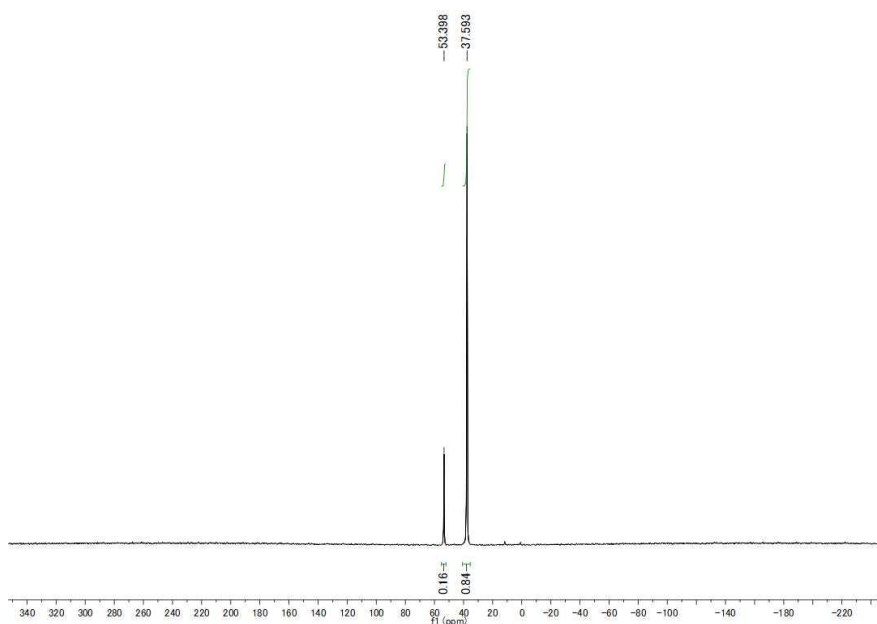


**<sup>31</sup>P NMR (60 °C, 6 h)**

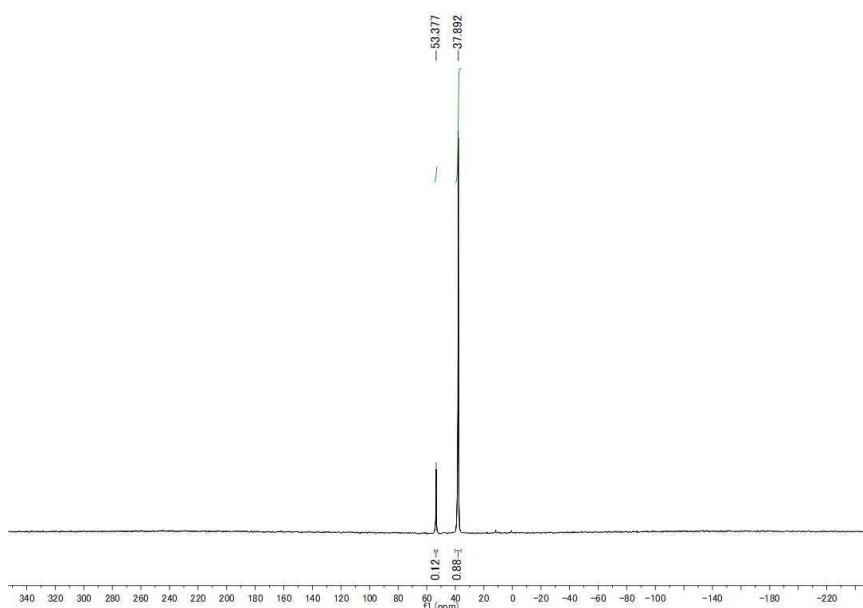


**Detailed Procedure for Entry 2 at Room Temperature:** The mixture of phosphonium salt  $\text{MeP}^+(\text{OMe})_3 \cdot \text{OTf}$  (**6c**) (121.8 mg, 0.42 mmol) and  $\text{H}_2\text{O}$  (8.3  $\mu\text{L}$ , 1.1 equiv.) in  $\text{CDCl}_3$  (0.5 mL) in an NMR tube sealed under  $\text{N}_2$  was slightly shaken at room temperature and measured by  $^{31}\text{P}$  NMR at 6 h, 19 h, and 24 h, respectively.  $^{31}\text{P}$  NMR spectra revealed that **3c** was formed in 79%, 84% and 88% yield, respectively.





**$^{31}\text{P}$  NMR (r.t., 19 h)**



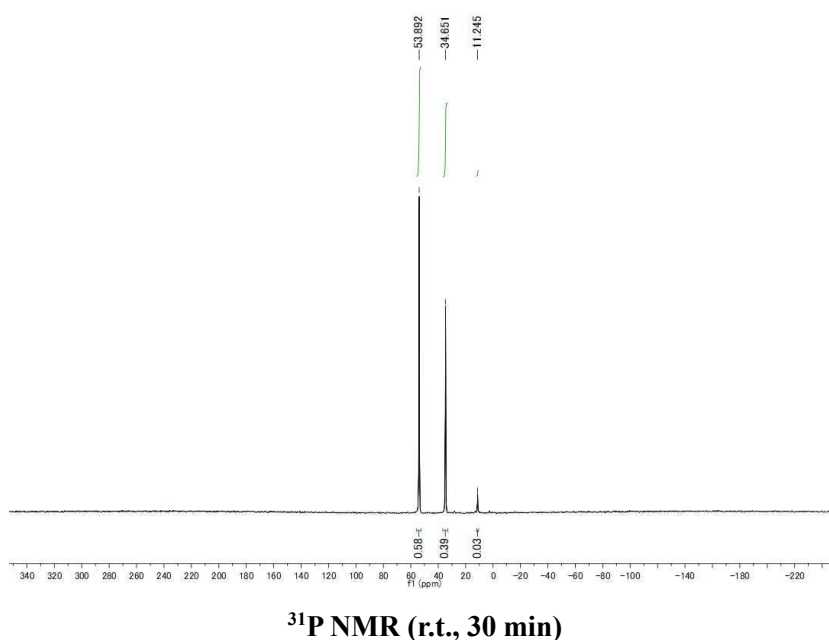
**$^{31}\text{P}$  NMR (r.t., 24 h)**

**Results and Discussion:** The above results indicated that, quite differently to the reactions of pure **6c** in  $\text{CDCl}_3$  without water (eq. 2-9) that reached the equilibrium (eq. 2-8) and gave close yields of **3c**, in the presence of 1.1 equiv. of water, the conversion of **6c** to **3c** can be much faster and give much higher yields of **3c**. This is most likely due to the removal of **4c** by the added water through hydrolysis (eq. 2-5). Hence, without the presence of **4c**, the equilibrium can be broken and driven rightward to ensure more efficient and faster

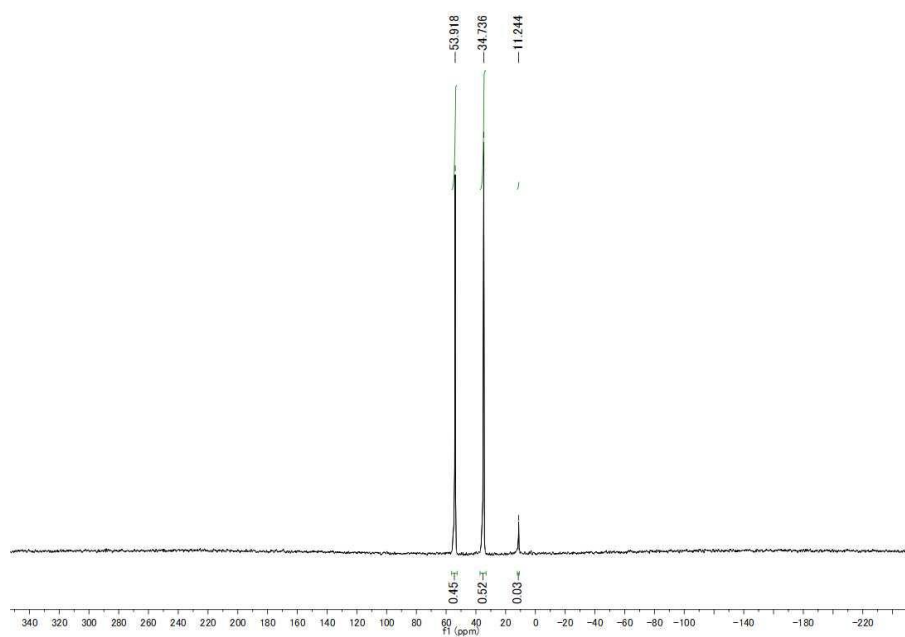
conversion of **6c** and higher yields of **3c**.

## 2-7-16. Conversion of not isolated $\text{MeP}^+(\text{OMe})_3 \cdot \text{OTf}$ (**6c**) to product **3c**

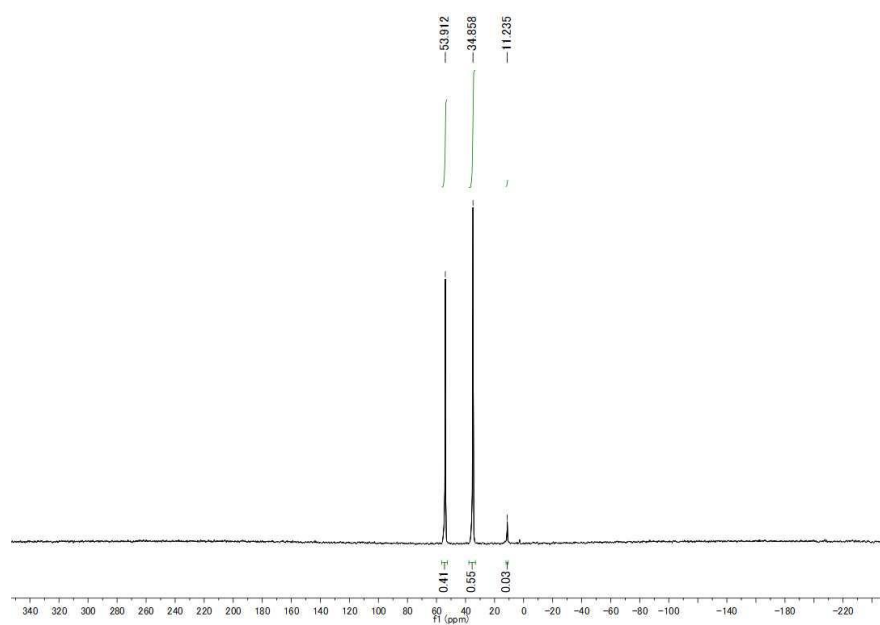
**Detailed procedure for Reaction at Room Temperature:** To an NMR tube cooled at 0 °C were successively added  $\text{CDCl}_3$  (0.5 mL), methyl trifluoromethanesulfonate (**4c**) (46.4  $\mu\text{L}$ , 0.424 mmol), and trimethyl phosphite (**1a**) (50  $\mu\text{L}$ , 1 equiv.) dropwise under  $\text{N}_2$ . The tube was then slowly warmed to room temperature and stirred for 30 min.  $^{31}\text{P}$  NMR spectra revealed that the reaction completed to afford **6c** in 58% NMR yield and **3c** in 39% NMR yield, respectively.



Without isolation of **6c**, the above reaction mixture (containing TfOMe **4c**) was directly shaken slightly at room temperature for 6 h, 21 h and 24h, respectively.  $^{31}\text{P}$  NMR spectra revealed that total yields of **3c** are 52%, 55% and 56% yields, respectively. This means the yields of **3c** generated from **6c** are 13%, 16%, and 17%, respectively.

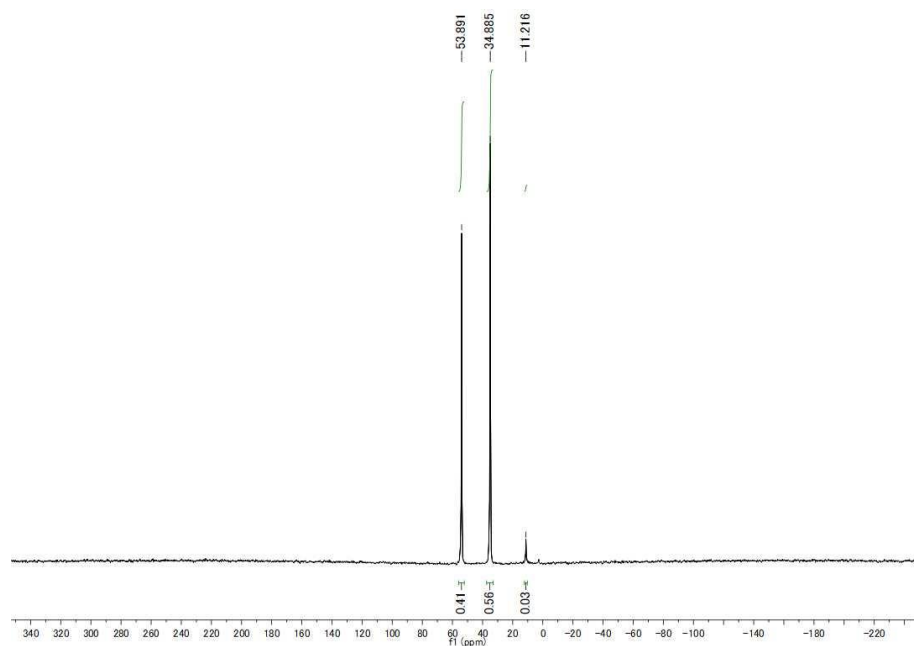


$^{31}\text{P}$  NMR (rt., 6 h)



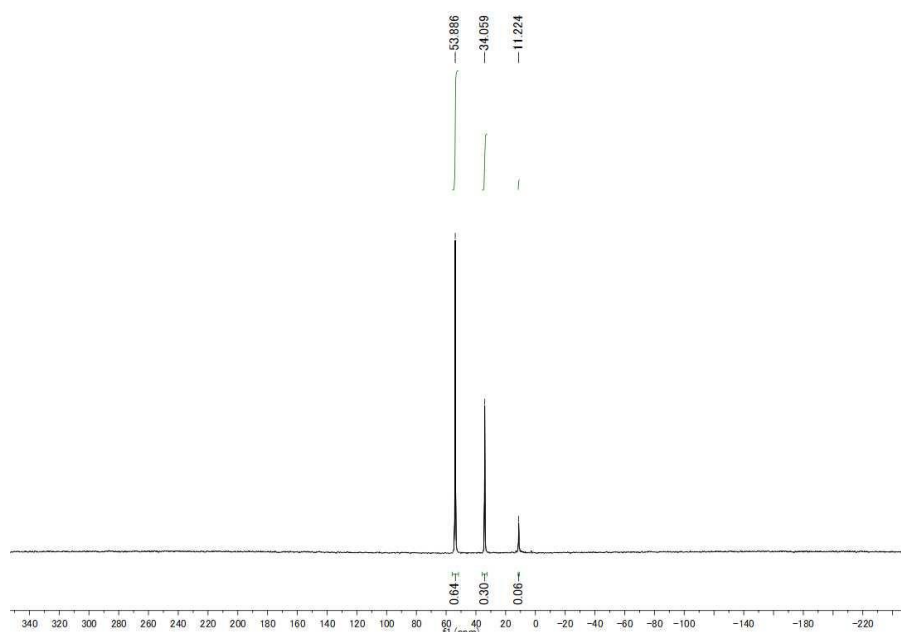
$^{31}\text{P}$  NMR (rt., 21 h)





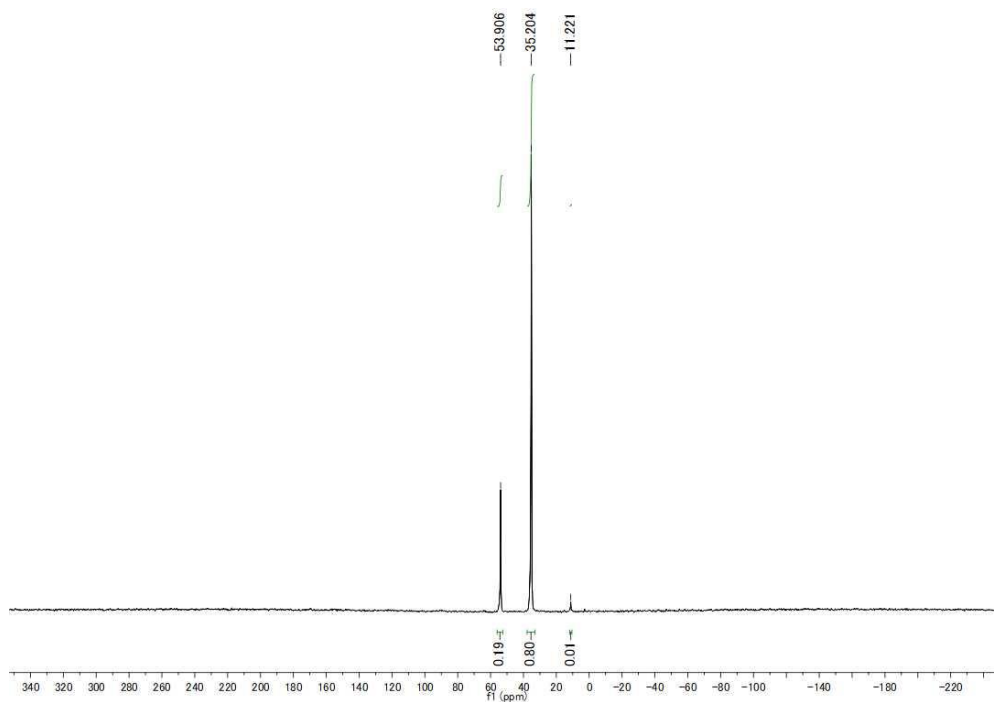
$^{31}\text{P}$  NMR (r.t., 24 h)

**Detailed Procedure for Reaction at 60 °C:** To an NMR tube cooled at 0 °C were successively added  $\text{CDCl}_3$  (0.5 mL), methyl trifluoromethanesulfonate (**4c**) (46.4  $\mu\text{L}$ , 0.424 mmol), and trimethyl phosphite (**1a**) (50  $\mu\text{L}$ , 1 equiv.) dropwise under  $\text{N}_2$ . The tube was then slowly warmed to room temperature and stirred for 30 min.  $^{31}\text{P}$  NMR spectra revealed that the reaction completed to afford **6c** in 64% NMR yield and **3c** in 30% NMR yield, respectively.

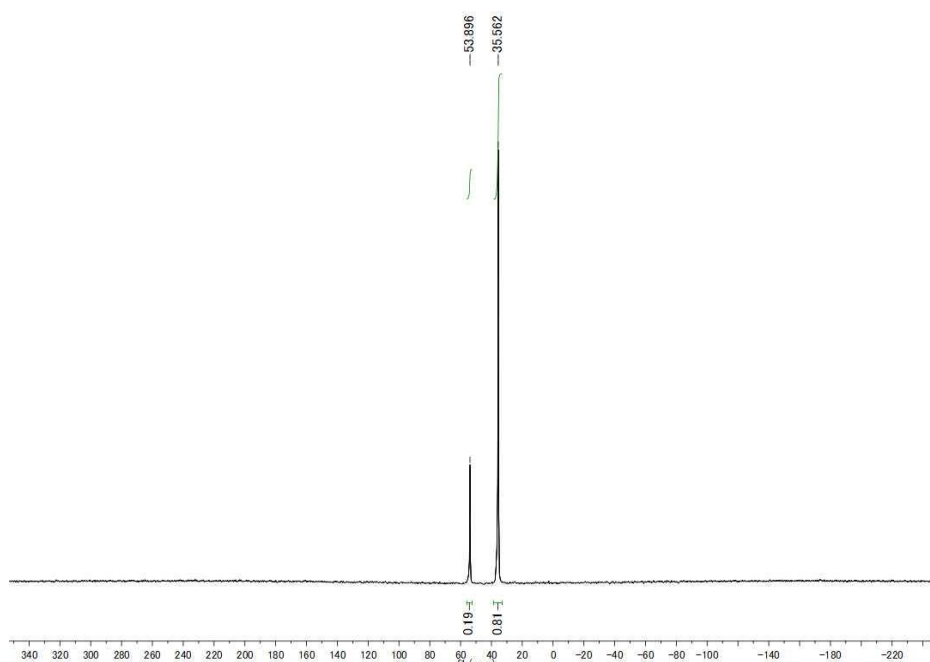


**$^{31}\text{P}$  NMR (r.t., 30 min)**

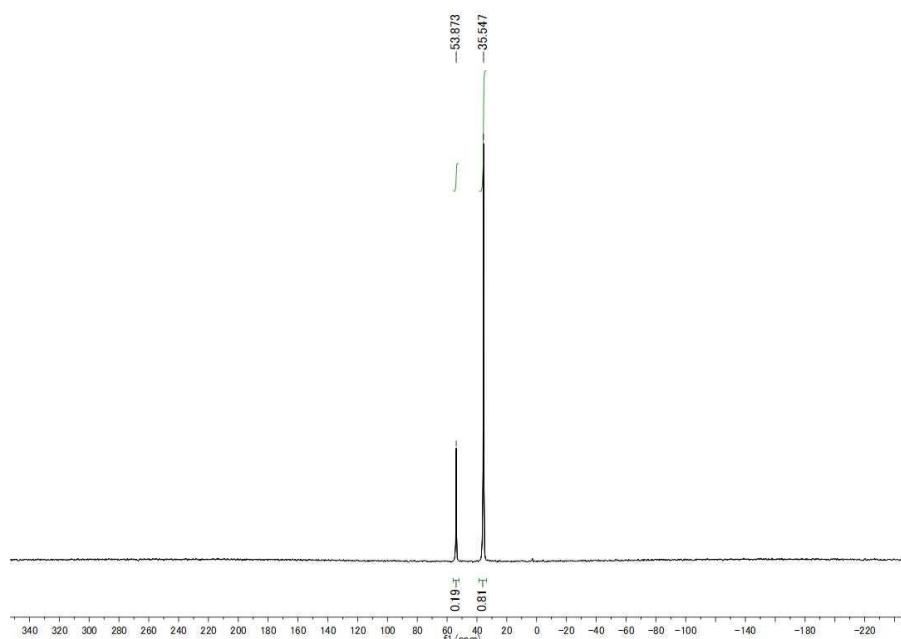
Without isolation of **6c**, the above reaction mixture (containing TfOMe **4c**) was directly heated at 60 °C for 6 h, 21 h and 24 h, respectively.  $^{31}\text{P}$  NMR spectra revealed that total yields of **3c** are 80%, 81%, and 81%, respectively. This means the yields of **3c** generated from **6c** are 50%, 51%, and 51%, respectively.



**$^{31}\text{P}$  NMR (60 °C, 6 h)**



**$^{31}\text{P}$  NMR (60 °C, 21 h)**



**$^{31}\text{P}$  NMR (60 °C, 24 h)**

**Results and Discussion:** Without isolation of **6c**, considerable amounts of TfOMe (**4c**) should be remained in the reaction mixture of **1c** and **4c**. Since **4c** can hinder the conversion of **6c** to **3c** by reacting with **3c** to give **6c** according to their equilibrium (eq. 8 in the main text), in the presence of the contaminant **4c** in the reaction mixture, conversion of **6c** to **3c** can be much slower in comparison with the reactions using pure **6c** (eq. 9). Even though, the close yields of **3c** (52~56% yields at room temperature; 80~81% yields at 60 °C) also revealed that both reactions have reached the equilibrium between **3c**, **4c**, and **6c** at 60 °C or at room temperature.

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- [6] (a) The reaction of  $P(OR)_3$  with Brønsted acids to give  $HP(O)(OR)_2$  has long been recognized, however, its synthetic applications, *catalytic hydrolysis in particular*, has not been fully explored: (a) Ref. 2b. (b) Walsh, E. N. *J. Am. Chem. Soc.* **1959**, *81*, 3023. (c) Nifant'ev, E. E. *Russ. Chem. Rev.* **1978**, *47*, 835. (d) Nitta, Y., Arakawa, Y., Ueyama, N. *Chem. Pharm. Bull.* **1986**, *34*, 2710. (e) Westheimer, F. H., Huang, S., Covitz, F. *J. Am. Chem. Soc.* **1988**, *110*, 181. (f) Tolstikova, L. L., Bel'skikh, A. V., Shainyan, B. A. *Russ. J. Gen. Chem.* **2011**, *81*, 474. (g) Truzzi, D. R., Franco, D. W. *Polyhedron* **2014**, *81*, 238.
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- [9] However, in the presence of water, water may work as the nucleophile to attack the MeO moiety of **5c** to directly give **2c**, MeOH, and TfOH, since  $TfO^-$  is known as a weak nucleophile<sup>15b-c</sup> and water can very possibly compete in this process. We are thankful to one of the reviewers for this proper and helpful suggestion.

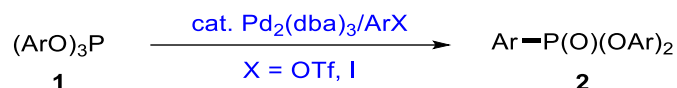
- [10] Stoichiometric reactions of  $P(OR)_3$  with  $TfOR$  were known. In addition to the mechanism suggested by Arbuzov (the monomolecular mechanism), Rumpf and Lewis successively proposed an autocatalytic mechanism (the bimolecular mechanism), though, they summarized that the monomolecular mechanism still exists in bimolecular mechanism dominated reactions: (a) Rumpf, P., *Bull. Soc. Chim. Fr.* **1951**, 18, 128. (b) Colle, K. S., Lewis, E. S. *J. Org. Chem.* **1978**, 43, 571. (c) Lewis, E. S., Colle, K. S. *J. Org. Chem.* **1981**, 46, 4369. (d) Lewis, E. S., Hamp, D. *J. Org. Chem.* **1983**, 48, 2025.
- [11] Non-catalytic reaction of P(III) esters with 7 equiv. of *p*-TsOMe generating rearranged products under harsh conditions was known: Artner, J., Ciesielski, M., Ahlmann, M., Walter, O., Döring, M., Perez, R. M., Altstädt, V., Sandler, J. K. W., ScharTEL, B. *Phosph., Sulfur, Silicon Relat. Elem.* **2007**, 182, 2131.
- [12] We also observed low conversions of **6c** to **3c** if **6c** prepared from  $P(OMe)_3$  (**1c**) and  $TfOMe$  (**4c**) (eq. 2-4) was not isolated from the reaction mixture but directly used in the reactions of eq. 9. 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. 2-7).
- [13] Indeed, as shown in Tables 2 and 3, the yields of product  $R-P(O)Z_2$  (**3**) are up to 98% yields.
- [14] The observed lower reaction efficiency and low products' yields of the sterically more bulky substrates (Table 2-4, 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.
- [15] Powder purchased from Sigma-Aldrich (495786) and used without further treatment.

## Chapter 3

# Palladium-Catalyzed the Michaelis-Arbuzov Rearrangement of $(\text{ArO})_3\text{P}$ to $\text{Ar-P}(\text{O})(\text{OAr})_2$

## Abstract

The first Pd-catalyzed Michaelis–Arbuzov rearrangement of triaryl phosphites to produce the corresponding aryl phosphonates in good to excellent yields is disclosed. This method is general as it can be readily extended to aryl phosphonites and phosphinites and a large gram-scale reaction with much lower loading of the catalyst. A plausible mechanism is proposed.



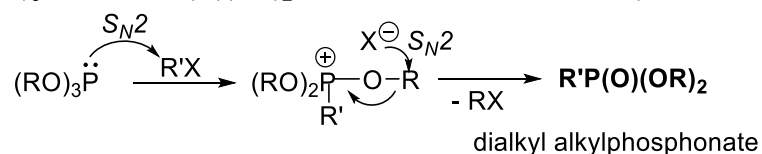
### 3-1. Introduction

Michaelis-Arbuzov reaction, the formation of P(V) phosphonates  $\text{RP}(\text{O})(\text{OR})_2$  by the rearrangement of P(III) phosphites via a combination of  $(\text{RO})_3\text{P}/\text{RX}$ , was discovered more than 120 years ago (Scheme 3-1).<sup>1</sup> Because the starting materials used in the reaction are readily available and also because the reaction process is simple, this reaction has been, ever since, the most famous and frequently used premier synthetic tool for the preparation of phosphonates  $\text{RP}(\text{O})(\text{OR})_2$ , that have important applications in organic synthesis, flame retardancy, material chemistry and biological chemistry.<sup>2</sup> However, the classic Michaelis-Arbuzov rearrangement is essentially restricted to the preparation of aliphatic phosphonates  $\text{RP}(\text{O})(\text{OR})_2$  as could be seen from its two sequential  $\text{S}_{\text{N}}2$  nucleophilic attack mechanism (Scheme 3-1(a)), i.e. the remained three phosphonates  $\text{ArP}(\text{O})(\text{OR})_2$ ,  $\text{RP}(\text{O})(\text{OAr})_2$  and  $\text{Ar}'\text{P}(\text{O})(\text{OAr})_2$ , that can have different properties and applications  $\text{RP}(\text{O})(\text{OR})_2$  does not have, could not be similarly prepared. In 1970, Tavs published an important modification to the classic Michaelis-Arbuzov reaction.<sup>3</sup> By using nickel catalysts, dialkyl arylphosphonate  $\text{ArP}(\text{O})(\text{OR})_2$  could be successfully prepared from the combination of  $(\text{RO})_3\text{P}/\text{ArX}$  (Scheme 3-1 (b)). Recent

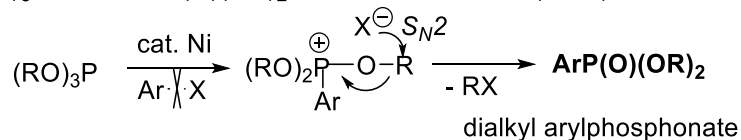
extensively studied reinvestigations on Michaelis-Arbuzov reaction also have led to certain progress for the preparation of  $\text{RP(O)(OAr)}_2$  from  $(\text{ArO})_3\text{P/RX}$  (Scheme 3-1(c)).<sup>4</sup> However, the most challenging preparation of  $\text{Ar}'\text{P(O)(OAr)}_2$  from  $(\text{ArO})_3\text{P/Ar}'\text{X}$  still remained unsolved yet, and these compounds have to be synthesized by a very tedious and heavy pollution stoichiometric Friedel-Crafts process using  $\text{PCl}_3$  (Scheme 3-1(d)).<sup>5</sup> The generation of the corresponding phosphonium intermediate is difficult because of the low nucleophilicity of  $(\text{ArO})_3\text{P}$  compared to  $(\text{RO})_3\text{P}$ . Moreover, the subsequent rearrangement of the phosphonium to  $\text{Ar}'\text{P(O)(OAr)}_2$  is also difficult since it requires a C-O bond cleavage by the catalyst.<sup>6</sup> Unlike Tavs system, the catalyst must well play a dual role in this transformation, that must be able to activate both the C-X bond and the C-O bond efficiently.

**Scheme 3-1** Michaelis-Arbuzov reaction for the preparation of phosphonates from the cheap phosphites and halides

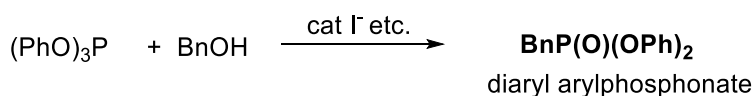
(a)  $(\text{RO})_3\text{P/R}'\text{X}$  to  $\text{R}'\text{P(O)(OR)}_2$ : Michaelis-Arbuzov reaction (1898-1906)



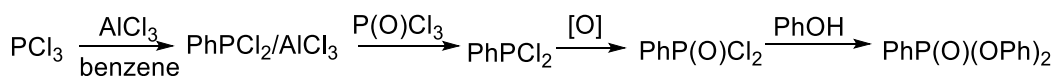
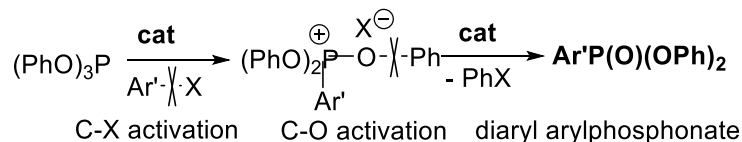
(b)  $(\text{RO})_3\text{P/ArX}$  to  $\text{ArP(O)(OR)}_2$ : Tavs's modification (1970)



(c)  $(\text{PhO})_3\text{P/RX}$  to  $\text{RP(O)(OPh)}_2$ : partially realized



(d)  $(\text{PhO})_3\text{P/Ar}'\text{X}$  to  $\text{Ar}'\text{P(O)(OPh)}_2$ : not realized



Current industrial process

## 3-2. Palladium-Catalyzed the Michaelis-Arbuzov Rearrangement of (ArO)<sub>3</sub>P to Ar–P(O)(OAr)<sub>2</sub>

### 3-2-1. Optimization of Reaction Conditions

Recently we reported a new TfOH-catalyzed Michaelis-Arbuzov rearrangement of (RO)<sub>3</sub>P to give phosphonate RP(O)(OR)<sub>2</sub> in high yields.<sup>7</sup> Unfortunately, like the classic Michaelis-Arbuzov reaction, this new reaction is also only applicable to alkyl phosphites, and no rearrangement took place at all with (ArO)<sub>3</sub>P. As shown in Table 3-1, the rearrangement product PhP(O)(OPh)<sub>2</sub> **2a** was not detected from a mixture of (PhO)<sub>3</sub>P **1a** and a catalytic amount of TfOH after heating at 160 °C for 16 h (run 1). No rearrangement took place either in the presence of Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>, Pd<sub>2</sub>(dba)<sub>3</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub> (runs 2-5). Very surprisingly, a combination of Pd(OAc)<sub>2</sub>/HOTf (run 6), could give 28% yield of PhP(O)(OPh)<sub>2</sub> under similar conditions. However, desperately, the yields of PhP(O)(OPh)<sub>2</sub> could not be further improved despite a heavy search on the experiment's conditions. In addition, changing Pd(OAc)<sub>2</sub> to other palladium complexes or other metals such as PdCl<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, Ni(OAc)<sub>2</sub>, NiCl<sub>2</sub>, Ni(cod)<sub>2</sub>, IrCl<sub>3</sub>, Rh(NO<sub>3</sub>)<sub>3</sub>, Rh(acac)<sub>2</sub>, RhCl(PPh<sub>3</sub>)<sub>3</sub>, Cu(OAc)<sub>2</sub>, Fe(acac)<sub>2</sub>, Zn(OTf)<sub>2</sub>, Bi(OTf)<sub>3</sub> etc. did not give promising positive results either. Very excitingly, excellent yields of the product **2a** were obtained by replacing HOTf with MeOTf (run 7) and PhOTf (run 8). Contrary to our expectation, a phosphine ligand dramatically retarded the reaction (runs 9-12), and no product **2a** was obtained using PdCl<sub>2</sub> (run 13), although other Pd(II) metals such as Pd(NO<sub>3</sub>)<sub>2</sub> and Pd(CF<sub>3</sub>CO<sub>2</sub>)<sub>2</sub> could catalyze the reaction. The Pd(0) complex Pd<sub>2</sub>(dba)<sub>3</sub> also efficiently catalyze the reaction to give 97% yield of **2a** (run 16). As to ROTf, in addition to PhOTf, others such as 1-naphtyl trifluoromethanesulfonate and 4-acetophenyl trifluoromethanesulfonate, and even TMSOTf (run 17) all could initiate the rearrangement and give high yields of **2a**. In addition to ROTf, PhI could also be used for this catalytic reaction (run 20). In contrast, PhBr (run 19) only sluggishly initiate the reaction and PhCl (run 18) could not initiate the reaction at all. The high temperature 160 °C is necessary under current neat conditions, otherwise the yield of **2a** decreased (run 21). Very interestingly, by carrying out the reaction in DMF, the reaction could efficiently take place even at 120 °C (run 24). DMF was the best solvent among other solvents such as toluene, DIF and NMP that only produce low yields of **2a**. Although sluggishly, the reaction even occurred at 80 °C (run 22), and 42% yield of **2a** could be obtained at 100 °C (run 23). Intriguingly, PhI seems superior to PhOTf under the current conditions, since



a trace of **2a** was obtained at 120 °C (run 25), and only 22% yield of **2a** was generated at 140 °C (run 26). Finally, unlike phosphines that retarded the reaction, the addition of a catalytic amount of R<sub>3</sub>N can accelerate the reaction. Therefore, excellent yields of PhP(O)(OPh)<sub>2</sub> **2a** could be obtained by the rearrangement of the cheap (PhO)<sub>3</sub>P **1a** by using a catalyst Pd<sub>2</sub>(dba)<sub>3</sub>/PhI/Et<sub>3</sub>N (run 27) or Pd<sub>2</sub>(dba)<sub>3</sub>/PhI/Cy<sub>2</sub>NMe (run 28).

**Table 3-1.** Palladium-catalyzed rearrangement of (PhO)<sub>3</sub>P to PhP(O)(OPh)<sub>2</sub><sup>a</sup>

$\begin{array}{c} \text{P(OPh)}_3 \\ \mathbf{1a} \end{array}$		$\xrightarrow{\text{cat. Pd/A/B}}$		$\text{PhP(O)(OPh)}_2 \\ \mathbf{2a}$
run	cat.	solvent	temp., time	yield(%) <sup>b</sup>
1	HOTf	none	160 °C, 16 h	none
2	Pd(OAc) <sub>2</sub>	none	160 °C, 16 h	none
3	PdCl <sub>2</sub>	none	160 °C, 16 h	none
4	Pd <sub>2</sub> (dba) <sub>3</sub>	none	160 °C, 16 h	none
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	none	160 °C, 16 h	none
6	Pd(OAc) <sub>2</sub> /HOTf	none	160 °C, 16 h	28
7	Pd(OAc) <sub>2</sub> /MeOTf	none	160 °C, 16 h	92
8	Pd(OAc) <sub>2</sub> /PhOTf	none	160 °C, 16 h	90
9	Pd(OAc) <sub>2</sub> /PhOTf/PPh <sub>3</sub>	none	160 °C, 16 h	trace
10	Pd(OAc) <sub>2</sub> /PhOTf/dppb	none	160 °C, 16 h	trace
11	Pd(OAc) <sub>2</sub> /PhOTf/dppp	none	160 °C, 16 h	trace
12	Pd(OAc) <sub>2</sub> /PhOTf/dppf	none	160 °C, 16 h	trace
13	PdCl <sub>2</sub> /PhOTf	none	160 °C, 16 h	none
14	Pd(NO <sub>3</sub> ) <sub>2</sub> /PhOTf	none	160 °C, 16 h	20
15	Pd(CF <sub>3</sub> CO <sub>2</sub> ) <sub>2</sub> /PhOTf	none	160 °C, 16 h	94
16	Pd <sub>2</sub> (dba) <sub>3</sub> /PhOTf	none	160 °C, 16 h	97
17	Pd <sub>2</sub> (dba) <sub>3</sub> /TMSOTf	none	160 °C, 16 h	85
18	Pd <sub>2</sub> (dba) <sub>3</sub> /PhCl	none	160 °C, 16 h	none
19	Pd <sub>2</sub> (dba) <sub>3</sub> /PhBr	none	160 °C, 16 h	19
20	Pd <sub>2</sub> (dba) <sub>3</sub> /PhI	none	160 °C, 16 h	62
21	Pd <sub>2</sub> (dba) <sub>3</sub> /PhI	none	140 °C, 16 h	26
22	Pd <sub>2</sub> (dba) <sub>3</sub> /PhI	DMF	80 °C, 21 h	trace
23	Pd <sub>2</sub> (dba) <sub>3</sub> /PhI	DMF	100 °C, 21 h	42
24	Pd <sub>2</sub> (dba) <sub>3</sub> /PhI	DMF	120 °C, 16 h	90
25	Pd <sub>2</sub> (dba) <sub>3</sub> /PhOTf	DMF	120 °C, 16 h	trace
26	Pd <sub>2</sub> (dba) <sub>3</sub> /PhOTf	DMF	140 °C, 16 h	92
27	Pd <sub>2</sub> (dba) <sub>3</sub> /PhI/Et <sub>3</sub> N	DMF	120 °C, 5 h	90
28	Pd <sub>2</sub> (dba) <sub>3</sub> /PhI/Cy <sub>2</sub> NMe	DMF	120 °C, 5 h	97

<sup>a</sup>Without using any solvent, a mixture of P(OPh)<sub>3</sub> (1a, 1.14 mmol), 5 mol % Pd catalyst (0.057 mmol), 5 mol % catalyst (0.057 mmol) and phosphine ligand (Pd/P = 1:2) were heated 160 °C for 16 h under N<sub>2</sub> in an NMR tube. <sup>b</sup>GC yield using dodecane as an internal standard.

### 3-2-2. Scope of Substrates

This new palladium-catalyzed Michaelis-Arbuzov type rearrangement is a rather general reaction. As shown in Table 3-2, in addition to aryl phosphonates, phosphinates, and phosphine oxides all could be prepared under

similar conditions. Thus, the aryl phosphonates **2** were obtained from the corresponding triaryl phosphites (runs 2-7). All the reactions with an electron-donating group (Me, *t*-Bu, MeO) took place efficiently to give the phosphonates in high yields. The bulky chemical **1g** bearing two methyl groups on the benzene ring could also be converted to corresponding phosphonate **2g** in 87% yield (entry 7). However, a substrate with an electron-withdrawing group, tris(4-fluorophenyl) phosphite **1f**, for example, only gave 31% yield of **2f** under similar conditions (entry 6). This transformation can also be readily extended to aryl phosphonites to synthesize the corresponding aryl phosphinates (entries 8-12). Thus, substrate with methyl, methoxyl and *tert*-butyl groups all give the corresponding products in good yields (entries 8-11). The halogen atom F was tolerable under the reaction conditions, although the yield from **1l** to **2l** was low (entry 12). Similarly, aryl phosphine oxides can be prepared by the isomerization of phosphinites in moderate yields (entries 13-19). Thus, a series of methyl-, methoxyl-, *tert*-butyl and fluoro-substituted phenyl diphenylphosphinites underwent isomerization to give the corresponding phosphine oxides in moderate yields (entries 14-17). Aliphatic phenyl dibutylphosphinite **1r** and the bulky phenyl dicyclohexylphosphinite **1s** also served well as the substrates to produce the corresponding phosphine oxides **2r** and **2s** in 82% and 66% yields, respectively (entries 18 and 19). Not restricted to phenylphosphites, other arylphosphites also underwent similar reactions to produce the corresponding phosphonates in excellent yields (entries 20-23).

**Table 3-2.** Scope of the Pd-catalyzed rearrangement of (ArO)PZ<sub>2</sub> to ArP(O)Z<sub>2</sub><sup>a</sup>

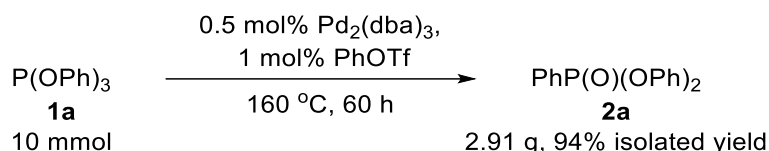
$(\text{ArO})\text{PZ}_2 \xrightarrow[160\text{ }^\circ\text{C, 16h}]{2.5\text{ mol\% Pd}_2(\text{dba})_3, 5\text{ mol\% PhOTf}} \text{Ar-P(O)Z}_2$		
run	(ArO)PZ <sub>2</sub> (1)	ArP(O)Z <sub>2</sub> (2) (isolated yield)
1	<b>1a</b> , R = H	<b>2a</b> , R = H, 93%
2	<b>1b</b> , R = 2-Me	<b>2b</b> , R = 2-Me, 92%
3	<b>1c</b> , R = 4-Me	<b>2c</b> , R = 4-Me, 91%
4	<b>1d</b> , R = 4-OMe	<b>2d</b> , R = 4-OMe, 95%
5	<b>1e</b> , R = 4- <i>t</i> Bu	<b>2e</b> , R = 4- <i>t</i> Bu, 94%
6 <sup>b</sup>	<b>1f</b> , R = 4-F	<b>2f</b> , R = 4-F, 31%
7	<b>1g</b> , R = 2,4-Me	<b>2g</b> , R = 2,4-Me, 87%
8	<b>1h</b> , R = H	<b>2h</b> , R = H, 80%
9	<b>1i</b> , R = 4-Me	<b>2i</b> , R = 4-Me, 53%
10 <sup>c</sup>	<b>1j</b> , R = 4-OMe	<b>2j</b> , R = 4-OMe, 50%
11	<b>1k</b> , R = 4- <i>t</i> Bu	<b>2k</b> , R = 4- <i>t</i> Bu, 58%
12 <sup>c</sup>	<b>1l</b> , R = 4-F	<b>2l</b> , R = 4-F, 37%
13 <sup>d</sup>	<b>1m</b> , R = H	<b>2m</b> , R = H, 64%
14 <sup>c</sup>	<b>1n</b> , R = 4-Me	<b>2n</b> , R = 4-Me, 54%
15 <sup>c</sup>	<b>1o</b> , R = 4-OMe	<b>2o</b> , R = 4-OMe, 51%
16 <sup>c</sup>	<b>1p</b> , R = 4- <i>t</i> Bu	<b>2p</b> , R = 4- <i>t</i> Bu, 68%
17 <sup>c</sup>	<b>1q</b> , R = 4-F	<b>2q</b> , R = 4-F, 33%
18 <sup>c</sup>	<b>1r</b> , R = <i>n</i> Bu	<b>2r</b> , R = <i>n</i> Bu, 82%
19 <sup>b</sup>	<b>1s</b> , R = Cy	<b>2s</b> , R = Cy, 66%
20	<b>1t</b>	<b>2t</b> , 92%
21 <sup>e</sup>	<b>1u</b>	<b>2u</b> , 91%
22	<b>1v</b> , R = H	<b>2v</b> , R = H, 91%
23	<b>1w</b> , R = 4-OMe	<b>2w</b> , R = 4-OMe, 93%

<sup>a</sup>Reaction conditions: 1.14 mmol of **1**, 2.5 mol % Pd<sub>2</sub>(dba)<sub>3</sub> and 5 mol % PhOTf were charged into an NMR tube and heated at 160 °C for 16 h under N<sub>2</sub>. <sup>b</sup>5 mol % Pd<sub>2</sub>(dba)<sub>3</sub> and 10 mol % PhOTf, 38 h. <sup>c</sup>5 mol % Pd<sub>2</sub>(dba)<sub>3</sub> and 10 mol % PhOTf. <sup>d</sup>38 h. <sup>e</sup>**1i** (0.2 mmol), 5 mol % PhI (0.01 mmol), 5 mol % Cy<sub>2</sub>NMe (0.01 mmol) and DMF (0.5 mL), 140 °C.

### 3-2-3. Synthetic Applications

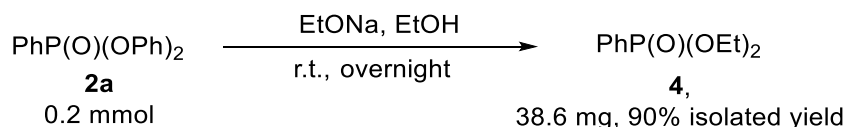
The synthetic usefulness of this new reaction was preliminarily demonstrated in Scheme 1. The expensive PhP(O)(OPh)<sub>2</sub><sup>8</sup> could be easily obtained in a high yield by simply heating the cheap (PhO)<sub>3</sub>P<sup>8</sup> in the presence of a trace amount of Pd<sub>2</sub>(dba)<sub>3</sub> (0.5 mol%) and PhOTf (1 mol%). Nearly 3 g of pure PhP(O)(OPh)<sub>2</sub> could be obtained from 10 mmol of (PhO)<sub>3</sub>P.

**Scheme 3-2.** Gram-scale preparation of PhP(O)(OPh)<sub>2</sub> from (PhO)<sub>3</sub>P



It is worth mentioning that the diphenyl phenylphosphonate **2a** could be easily transferred to diethyl phenylphosphonate **4** in 90% isolated yield through ester exchange<sup>9</sup> as demonstrated by the examples shown in Scheme 3-3.

**Scheme 3-3.** Synthetic applications of diphenyl phenylphosphonate **2a**

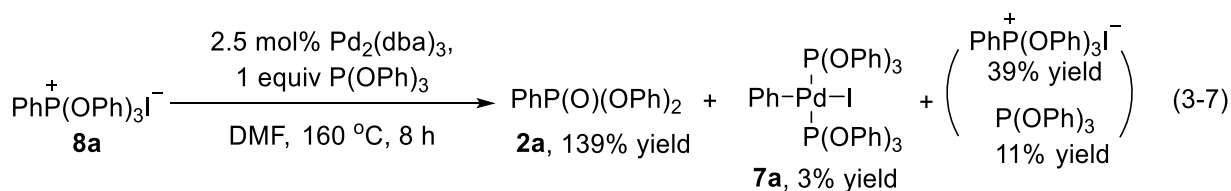
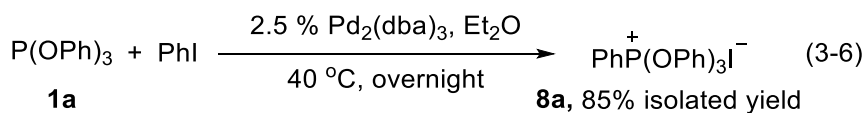
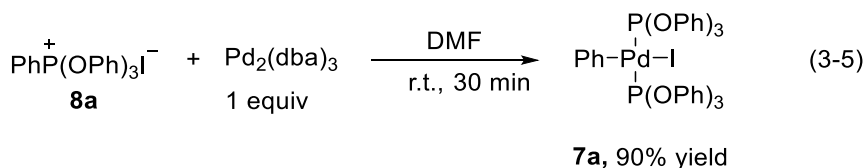
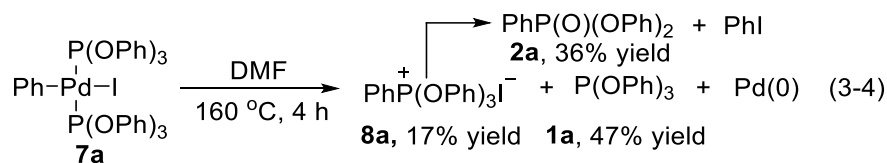
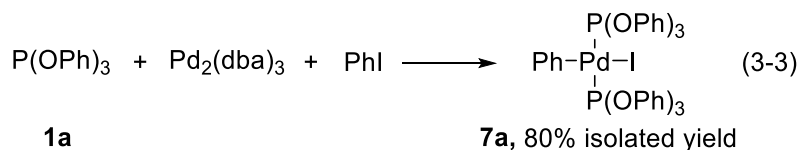
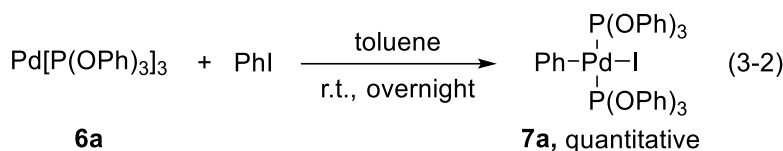
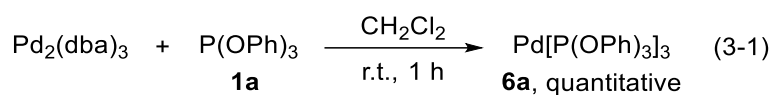


## 3-3. Mechanistic Studies

### 3-3-1. Control Experiments

To probe the reaction mechanism, control reactions were conducted. Firstly, treatment of P(OPh)<sub>3</sub> (**1a**) with Pd<sub>2</sub>(dba)<sub>3</sub> quickly generated quantitative of Pd[P(OPh)<sub>3</sub>]<sub>3</sub> (**6a**) (eq. 3-1).<sup>10</sup> Then, the oxidative addition of **6a** to iodobenzene produced palladium-aryl complex **7a** quantitatively at room temperature (eq. 3-2).<sup>11</sup> This

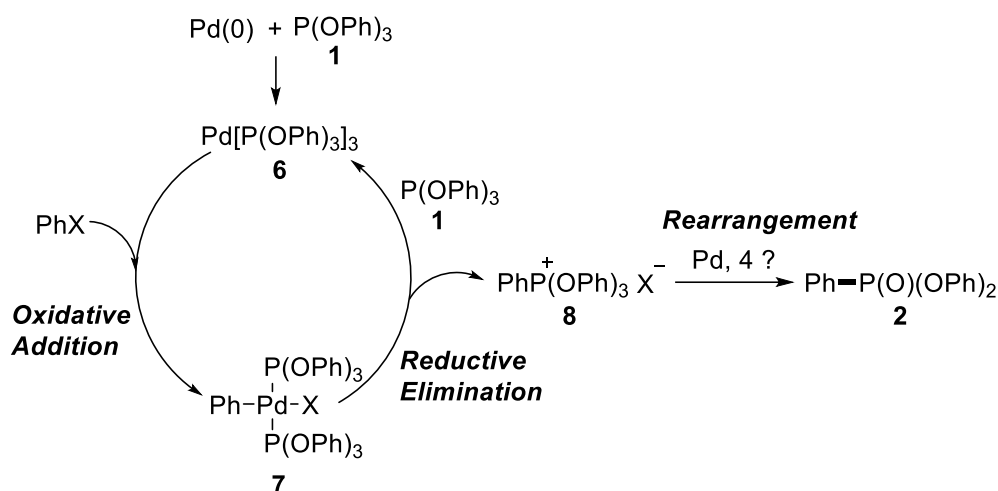
reaction can be achieved in one pot. Thus,  $\text{Pd}_2(\text{dba})_3$  reacted with a mixture of  $\text{PhI}$  and **1a** smoothly at room temperature to produce **7a** in 80% isolated yield (eq. 3-3). Interestingly, **7a** could easily decompose to phosphonium salt  $\text{PhP}^+(\text{OPh})_3\text{I}^-$  **8a**, **1a** and  $\text{Pd}(0)$  in DMF at 160 °C for 4 h (eq. 3-4). Moreover, phosphonium salt **8a** could also react with  $\text{Pd}_2(\text{dba})_3$  fastly to give a high yield of **7a** (eq. 3-5). There is an equilibrium between **7a**, **8a** and Palladium. In addition, the reaction of **1a** and  $\text{PhI}$  catalyzed by  $\text{Pd}_2(\text{dba})_3$  in  $\text{Et}_2\text{O}$  also precipitated to afford phosphonium salt **8a** in 85% isolated yield at 40 °C for overnight (eq. 3-6). From eq. 3-7, we can observe that the decomposition of phosphonium salt **8a** may take place via C–O activation by Pd to give **2a** and **7a**.



### 3-3-2. Proposed Mechanism

As shown in Scheme 3-4, a possible mechanism was proposed. Thus, Pd(0) firstly coordinated with **1** to give a new palladium species Pd(0) **6**, which then underwent oxidative addition with PhX (X = I, OTf) to give palladium-aryl complex Pd(II) **7**. Then reductive elimination of **7** took place to afford phosphonium salt **8** and regenerate Pd(0) **6**. The exact mechanism for the conversion of **8** to **2** is not clear. It may take place via C–O activation by Pd to give **2**.

**Scheme 3-4.** Proposed mechanism for the Pd-catalyzed  $sp^2C$ –O cleavage reactions of P(III) esters



### 3-4. Conclusions

In summary, I have developed a novel and efficient method to prepare aryl phosphonates from the  $sp^2C$ –O cleavage reaction of aryl phosphites catalyzed by a palladium and PhX (X = OTf, I) to afford the corresponding rearrangement products in good to excellent yields. Those methods are general in substrate scope as it can be readily extended to aryl phosphonites and phosphinites for synthesizing the corresponding aryl phosphinates and phosphine oxides.

## 3-5. Experimental Section

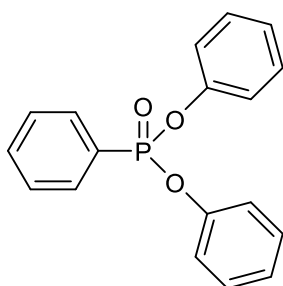
### 3-5-1. General Information

Unless otherwise noted, small scale reactions were carried out in NMR tubes under N<sub>2</sub> atmosphere and solvent-free condition. Dry solvents were obtained according to standard procedures. Unless otherwise noted, all reagents were purchased and used as received. Trivalent phosphorus compounds were either purchased

(from TCI if commercially available) or prepared from the corresponding alcohols and phosphorus (III) chloride according to the literature procedure (P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix, C. Mioskowski, *Angew. Chem. Int. Ed.* **2003**, 42, 2389). Product **2** were purified by a preparative GPC apparatus (JAPAN ANALYTICAL INDUSTRY LC-908 with JAIGEL-1H, polystyrene-based column) using CHCl<sub>3</sub> as the eluent (smaller scale reactions). Quaternary phosphonium salt PhP<sup>+</sup>(OPh)<sub>3</sub>·I (**8a**) used in the control reactions was obtained in 85% isolated yield according to the literature method (D. Marcoux, A. B., Charette, *J. Org. Chem.* **2008**, 73, 590). <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR spectra of the products were acquired on a JEOL JNM-ECS400 (400 MHz for <sup>1</sup>H, 100 MHz for <sup>13</sup>C, and 162 MHz for <sup>31</sup>P NMR spectroscopy). Chemical shifts for <sup>1</sup>H NMR are referred to internal Me<sub>4</sub>Si (0 ppm) and reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Chemical shifts for <sup>31</sup>P NMR were relative to H<sub>3</sub>PO<sub>4</sub> (85% solution in D<sub>2</sub>O, 0 ppm).

### 3-5-2. Typical procedure for Pd-catalyzed transformation of (ArO)<sub>3</sub>P to Ar-P(O)(OAr)<sub>2</sub>

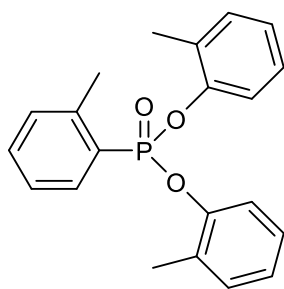
To an NMR tube was added triphenyl phosphite (**1a**) (0.3 mL, 1.14 mmol), 2.5 mol% Pd<sub>2</sub>(dba)<sub>3</sub> and 5 mol% PhOTf under N<sub>2</sub>. The tube was then heated at 160 °C for 16 h and **1a** was totally consumed. Pure **2a** was obtained by preparative GPC in 93% isolated yield.



#### Diphenyl phenylphosphonate (**2a**)

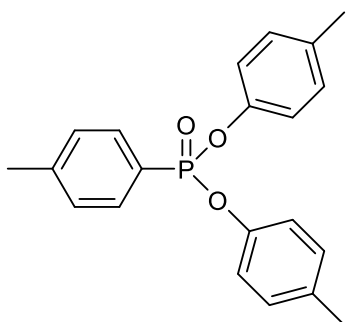
White solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) : δ 7.99-7.94 (m, 2H), δ 7.61-7.58 (m, 1H), δ 7.52-7.47 (m, 2H), δ 7.30-7.25 (m, 4H), δ 7.20-7.11 (m, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 150.5 (d, J<sub>C-P</sub> = 7.4 Hz), 133.3 (d, J<sub>C-P</sub> = 2.6 Hz), 132.4 (d, J<sub>C-P</sub> = 10.4 Hz), 129.8, 128.7 (d, J<sub>C-P</sub> = 15.8 Hz), 127.0 (d, J<sub>C-P</sub> = 191.7 Hz), 125.2, 120.7 (d, J<sub>C-P</sub> = 4.5 Hz). <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>): δ 12.32.





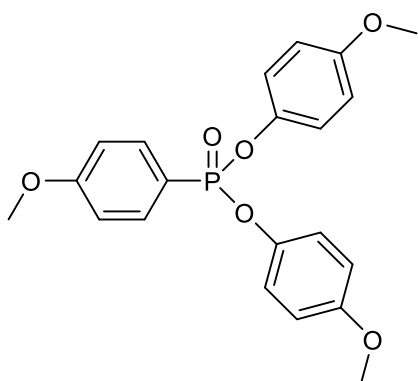
**1-Methyl-2-[(2-methylphenoxy)-(2-methylphenyl)phosphoryl]oxybenzene (2b)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) :  $\delta$  8.16-8.11 (m, 1H),  $\delta$  7.53-7.49 (m, 1H),  $\delta$  7.36-7.31 (m, 2H),  $\delta$  7.22-7.17 (m, 4H),  $\delta$  7.11-7.03 (m, 4H), 2.78 (d,  $J = 1.2$  Hz, 3H), 1.32 (s, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.3 (d,  $J_{\text{C-P}} = 8.0$  Hz), 142.2 (d,  $J_{\text{C-P}} = 10.9$  Hz), 134.3 (d,  $J_{\text{C-P}} = 11.0$  Hz), 133.3 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.7 (d,  $J_{\text{C-P}} = 15.9$  Hz), 131.5, 129.6 (d,  $J_{\text{C-P}} = 5.5$  Hz), 126.8 (d,  $J_{\text{C-P}} = 188.2$  Hz), 127.0, 125.9 (d,  $J_{\text{C-P}} = 15.5$  Hz), 125.0, 120.5 (d,  $J_{\text{C-P}} = 2.6$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.08. HRMS (ESI-TOF):  $m/z$ : ( $[\text{M}+\text{Na}]^+$ ) Calcd. for  $\text{C}_{21}\text{H}_{21}\text{NaO}_3\text{P}$  375.1126, Found 375.1099.



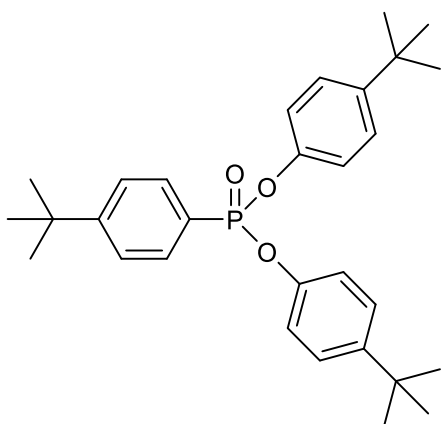
***p*-Tolyl-phosphonic acid di-*p*-tolyl ester (2c)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.85-7.80 (m, 2H),  $\delta$  7.29-7.25 (m, 2H),  $\delta$  7.06 (s, 8H),  $\delta$  2.39 (s, 3H),  $\delta$  2.27 (s, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.3 (d,  $J_{\text{C-P}} = 7.5$  Hz), 143.8, 134.6, 132.4 (d,  $J_{\text{C-P}} = 10.6$  Hz), 130.2, 129.4 (d,  $J_{\text{C-P}} = 16.1$  Hz), 123.8 (d,  $J_{\text{C-P}} = 193.3$  Hz), 120.4 (d,  $J_{\text{C-P}} = 4.1$  Hz), 21.8, 20.8.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.26.



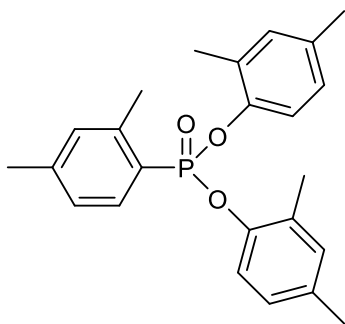
**Bis(4-methoxyphenyl) (4-methoxyphenyl)phosphonate (2d).**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.86-7.80 (m, 2H),  $\delta$  7.09-7.06 (m, 4H), 6.95-6.92 (m, 2H),  $\delta$  6.78-6.73 (m, 4H),  $\delta$  3.78 (s, 3H),  $\delta$  3.69 (s, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.4 (d,  $J_{\text{C-P}} = 3.4$  Hz), 156.7, 144.1 (d,  $J_{\text{C-P}} = 7.4$  Hz), 134.5 (d,  $J_{\text{C-P}} = 11.9$  Hz), 121.6 (d,  $J_{\text{C-P}} = 4.3$  Hz), 118.0 (d,  $J_{\text{C-P}} = 198.1$  Hz), 114.7, 114.2 (d,  $J_{\text{C-P}} = 16.6$  Hz), 55.6, 55.4.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.10. HRMS (ESI-TOF):  $m/z$ : ( $[\text{M}+\text{H}]^+$ ) Calcd. for  $\text{C}_{21}\text{H}_{22}\text{O}_6\text{P}$  401.1154, Found 401.1134.



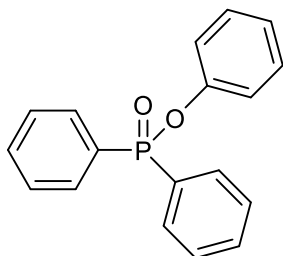
**Bis(4-(tert-butyl)phenyl) (4-(tert-butyl)phenyl)phosphonate (2e)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.94-7.88 (m, 2H), 7.53-7.50 (m, 2H), 7.29-7.25 (m, 4H), 7.12-7.09 (m, 4H), 1.34 (s, 9H), 1.27 (s, 18H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.8, 148.3 (d,  $J_{\text{C-P}} = 7.8$  Hz), 147.8, 132.2 (d,  $J_{\text{C-P}} = 10.7$  Hz), 126.6, 125.7 (d,  $J_{\text{C-P}} = 15.8$  Hz), 124.2 (d,  $J_{\text{C-P}} = 195.2$  Hz), 120.1 (d,  $J_{\text{C-P}} = 4.4$  Hz), 35.2, 34.4, 31.5, 31.2.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.09. HRMS (ESI-TOF):  $m/z$ : ( $[\text{M}+\text{Na}]^+$ ) Calcd. for  $\text{C}_{30}\text{H}_{39}\text{O}_3\text{NaP}$  501.2535, Found 501.2523.



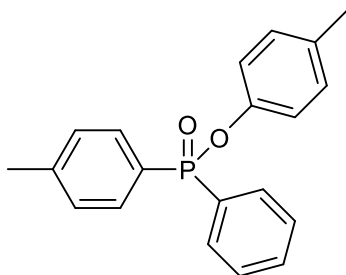
**Bis(2,4-dimethylphenyl) (2,4-dimethylphenyl)phosphonate (2g)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.02-7.97 (m, 1H), 7.15-7.11 (m, 2H), 7.07 (d,  $J = 8.0$  Hz, 2H), 6.97 (s, 2H), 6.87 (d,  $J = 8.4$  Hz, 2H), 2.72 (s, 3H), 2.38 (s, 3H), 2.25 (s, 6H), 2.21 (s, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  147.2 (d,  $J_{\text{C-P}} = 8.3$  Hz), 143.7 (d,  $J_{\text{C-P}} = 3.2$  Hz), 142.0 (d,  $J_{\text{C-P}} = 10.8$  Hz), 134.5 (d,  $J_{\text{C-P}} = 11.2$  Hz), 134.3, 132.5 (d,  $J_{\text{C-P}} = 16.2$  Hz), 132.0, 129.2 (d,  $J_{\text{C-P}} = 5.6$  Hz), 127.4, 126.5 (d,  $J_{\text{C-P}} = 16.0$  Hz), 123.7 (d,  $J_{\text{C-P}} = 190.1$  Hz), 120.2 (d,  $J_{\text{C-P}} = 2.6$  Hz), 21.7, 21.6, 20.8, 16.8.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.99. HRMS (ESI-TOF):  $m/z$ :  $([\text{M}+\text{H}]^+)$  Calcd. for  $\text{C}_{24}\text{H}_{28}\text{O}_3\text{P}$  395.1776, Found 395.1756.



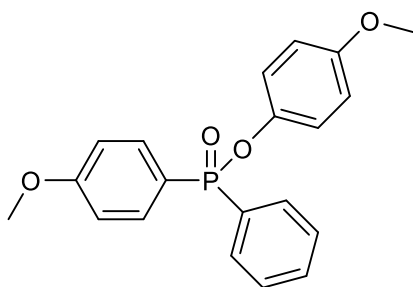
**Phenyl diphenylphosphinate (2h).**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.91-7.86 (m, 4H), 7.53-7.49 (m, 2H), 7.47-7.42 (m, 4H), 7.25-7.18 (m, 4H), 7.07-7.04 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  151.0 (d,  $J_{\text{C-P}} = 8.2$  Hz), 132.5 (d,  $J_{\text{C-P}} = 2.5$  Hz), 131.9 (d,  $J_{\text{C-P}} = 10.2$  Hz), 131.1 (d,  $J_{\text{C-P}} = 137.8$  Hz), 129.7, 128.7 (d,  $J_{\text{C-P}} = 13.3$  Hz), 124.7, 120.8 (d,  $J_{\text{C-P}} = 4.8$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.98. This compound was known: W. Peng, M. S. Jean'ne. *J. Fluorine Chem.* **2005**, 126, 1054.



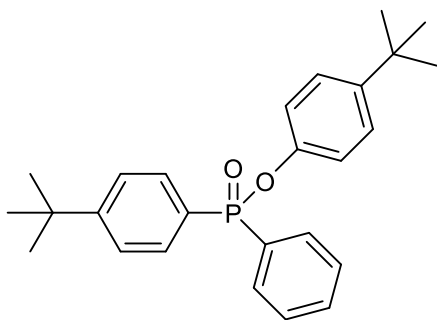
***p*-Tolyl phenyl(*p*-tolyl)phosphinate (2i).**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.89-7.84 (m, 2H), 7.76 (dd,  $J = 8.0$  Hz, 12.4 Hz, 2H), 7.51-7.47 (m, 1H), 7.45-7.40 (m, 2H), 7.26-7.23 (m, 2H), 7.08-6.99 (m, 4H), 2.36 (s, 3H), 2.23 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.8 (d,  $J_{\text{C-P}} = 8.3$  Hz), 143.1 (d,  $J_{\text{C-P}} = 2.6$  Hz), 134.1, 132.3 (d,  $J_{\text{C-P}} = 2.5$  Hz), 132.0 (d,  $J_{\text{C-P}} = 10.8$  Hz), 131.8 (d,  $J_{\text{C-P}} = 10.4$  Hz), 129.0 (d,  $J_{\text{C-P}} = 374.2$  Hz), 130.1, 129.5, 129.3, 128.6 (d,  $J_{\text{C-P}} = 13.3$  Hz), 120.5 (d,  $J_{\text{C-P}} = 4.6$  Hz), 21.7, 20.8.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  31.29. HRMS (ESI-TOF):  $m/z$ : ( $[\text{M}+\text{Na}]^+$ ) Calcd. for  $\text{C}_{20}\text{H}_{19}\text{NaO}_2\text{P}$  345.1020, Found 345.0991.



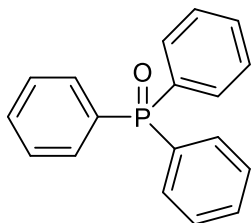
**4-Methoxyphenyl (4-methoxyphenyl)(phenyl)phosphinate (2j).**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.87-7.77 (m, 4H), 7.51-7.40 (m, 3H), 7.08 (d,  $J = 8.8$  Hz, 2H), 6.94 (dd,  $J = 2.8$  Hz, 8.8 Hz, 2H), 6.72 (d,  $J = 8.8$  Hz, 2H), 3.81 (m, 3H), 3.70 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.9 (d,  $J_{\text{C-P}} = 2.7$  Hz), 156.4, 144.5 (d,  $J_{\text{C-P}} = 8.2$  Hz), 134.0 (d,  $J_{\text{C-P}} = 11.5$  Hz), 131.7 (d,  $J_{\text{C-P}} = 138.7$  Hz), 132.3 (d,  $J_{\text{C-P}} = 2.6$  Hz), 131.7 (d,  $J_{\text{C-P}} = 110.0$  Hz), 128.6 (d,  $J_{\text{C-P}} = 13.3$  Hz), 122.1 (d,  $J_{\text{C-P}} = 143.8$  Hz), 121.7 (d,  $J_{\text{C-P}} = 4.5$  Hz), 114.6, 114.2 (d,  $J_{\text{C-P}} = 14.4$  Hz), 55.5 (d,  $J_{\text{C-P}} = 18.8$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  31.58.



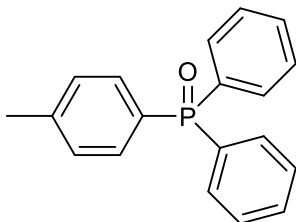
**4-(*Tert*-butyl)phenyl (4-(*tert*-butyl)phenyl)(phenyl)phosphinate (2k).**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.91-7.79 (m, 4H), 7.50-7.41 (m, 5H), 7.23 (d,  $J = 8.8$  Hz, 2H), 7.09 (d,  $J = 8.8$  Hz, 2H), 1.31 (s, 9H), 1.24 (m, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.0 (d,  $J_{\text{C-P}} = 2.7$  Hz), 148.7 (d,  $J_{\text{C-P}} = 8.1$  Hz), 147.3, 131.7 (d,  $J_{\text{C-P}} = 137.0$  Hz), 132.3 (d,  $J_{\text{C-P}} = 2.4$  Hz), 131.9 (d,  $J_{\text{C-P}} = 17.2$  Hz), 131.8 (d,  $J_{\text{C-P}} = 17.5$  Hz), 128.2 (d,  $J_{\text{C-P}} = 140.7$  Hz), 128.6 (d,  $J_{\text{C-P}} = 13.2$  Hz), 126.5, 125.7 (d,  $J_{\text{C-P}} = 13.7$  Hz), 120.2 (d,  $J_{\text{C-P}} = 4.6$  Hz), 34.7 (d,  $J_{\text{C-P}} = 76.3$  Hz), 31.3 (d,  $J_{\text{C-P}} = 29.4$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  31.17.



**Triphenylphosphine oxide (2m).**

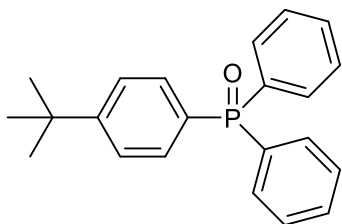
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.65-7.60 (m, 6H), 7.49-7.37 (m, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  133.2, 132.2 (d,  $J_{\text{C-P}} = 9.6$  Hz), 132.0 (d,  $J_{\text{C-P}} = 2.5$  Hz), 128.6 (d,  $J_{\text{C-P}} = 12.0$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.58.



**4-Methylphenyl diphenylphosphine oxide (2n).**

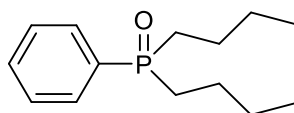
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.67-7.62 (m, 4H), 7.56-7.48 (m, 4H), 7.44-7.40 (m, 4H), 7.25-7.23 (m, 2H), 2.37 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  142.6 (d,  $J_{\text{C-P}} = 2.5$  Hz), 132.8 (d,  $J_{\text{C-P}} = 105.9$

Hz), 132.2 (d,  $J_{C-P}$  = 10.2 Hz), 132.1 (d,  $J_{C-P}$  = 9.6 Hz), 131.9 (d,  $J_{C-P}$  = 2.4 Hz), 129.3 (d,  $J_{C-P}$  = 12.5 Hz), 129.1 (d,  $J_{C-P}$  = 120.0 Hz), 128.5 (d,  $J_{C-P}$  = 12.1 Hz), 21.7.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.05.



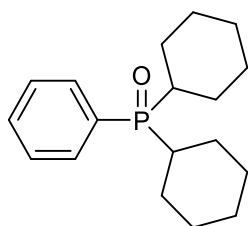
**4-(Tert-butyl)phenyl diphenylphosphine oxide (2p).**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.69-7.64 (m, 4H), 7.60-7.51 (m, 4H), 7.47-7.42 (m, 6H), 1.32 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  155.5, 132.8 (d,  $J_{C-P}$  = 103.6 Hz), 132.1 (d,  $J_{C-P}$  = 9.7 Hz), 132.0 (d,  $J_{C-P}$  = 10.2 Hz), 131.9 (d,  $J_{C-P}$  = 2.6 Hz), 129.2 (d,  $J_{C-P}$  = 94.3 Hz), 128.5 (d,  $J_{C-P}$  = 12.2 Hz), 125.6 (d,  $J_{C-P}$  = 12.0 Hz), 35.1, 31.2.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.79.



**Dibutyl phenyl phosphate (2r).**

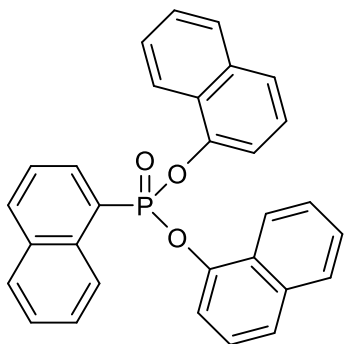
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.70-7.65 (m, 2H), 7.51-7.45 (m, 3H), 2.00-1.78 (m, 4H), 1.61-1.55 (m, 2H), 1.45-1.32 (m, 6H), 0.87-0.83 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  132.6 (d,  $J_{C-P}$  = 91.9 Hz), 131.5, 130.4 (d,  $J_{C-P}$  = 8.6 Hz), 128.6 (d,  $J_{C-P}$  = 10.9 Hz), 29.7 (d,  $J_{C-P}$  = 68.1 Hz), 24.1 (d,  $J_{C-P}$  = 14.3 Hz), 23.5 (d,  $J_{C-P}$  = 3.5 Hz), 13.6.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  41.24.



**Di(cyclohexyl)phenylphosphine oxide (2s)**

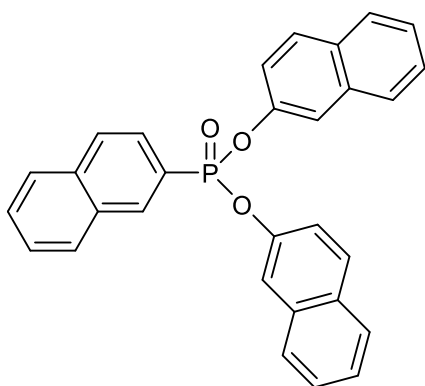
White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.66-7.61 (m, 2H), 7.49-7.42 (m, 3H), 2.02-2.00 (m, 4H), 1.79-1.57 (m, 8H), 1.28-1.10 (m, 10H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  131.5 (d,  $J_{C-P}$  = 7.5 Hz), 131.3 (d,  $J_{C-P}$  = 2.5 Hz), 130.1 (d,  $J_{C-P}$  = 84.8 Hz), 128.3 (d,  $J_{C-P}$  = 10.4 Hz), 35.2 (d,  $J_{C-P}$  = 66.9 Hz),

26.5 (d,  $J_{C-P} = 23.7$  Hz), 26.5, 25.9, 25.6 (d,  $J_{C-P} = 1.8$  Hz), 24.7 (d,  $J_{C-P} = 2.7$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  45.67.



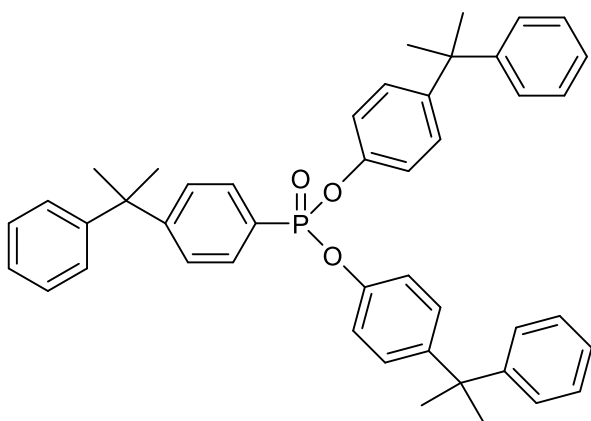
**Di(naphthalen-1-yl) naphthalen-1-ylphosphonate (2t)**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.11 (d,  $J = 8.4$  Hz, 1H), 8.59 (dd,  $J = 7.2$  Hz, 17.6 Hz, 1H), 8.15 (d,  $J = 8.4$  Hz, 2H), 8.11 (d,  $J = 8.0$  Hz, 1H), 7.94 (d,  $J = 8.0$  Hz, 1H), 7.82 (d,  $J = 8.0$  Hz, 2H), 7.72 (t,  $J = 7.2$  Hz, 15.6 Hz, 1H), 7.65-7.56 (m, 6H), 7.50-7.41 (m, 4H), 7.34 (t,  $J = 7.6$  Hz, 16.0 Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  146.8 (d,  $J_{C-P} = 8.2$  Hz), 135.5 (d,  $J_{C-P} = 9.9$  Hz), 135.0, 134.9 (d,  $J_{C-P} = 3.5$  Hz), 133.9 (d,  $J_{C-P} = 13.6$  Hz), 132.8 (d,  $J_{C-P} = 11.5$  Hz), 129.3, 128.3, 127.9, 127.0, 126.8 (d,  $J_{C-P} = 19.1$  Hz), 126.8, 126.7, 126.5, 125.6, 125.2, 124.8 (d,  $J_{C-P} = 17.8$  Hz), 123.9 (d,  $J_{C-P} = 188.2$  Hz), 122.0, 115.6 (d,  $J_{C-P} = 3.3$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.62. HRMS (ESI-TOF):  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd. for  $\text{C}_{30}\text{H}_{21}\text{NaO}_3\text{P}$  483.1126, Found 483.1101.



**Di(naphthalen-2-yl) naphthalen-2-ylphosphonate (2u).**

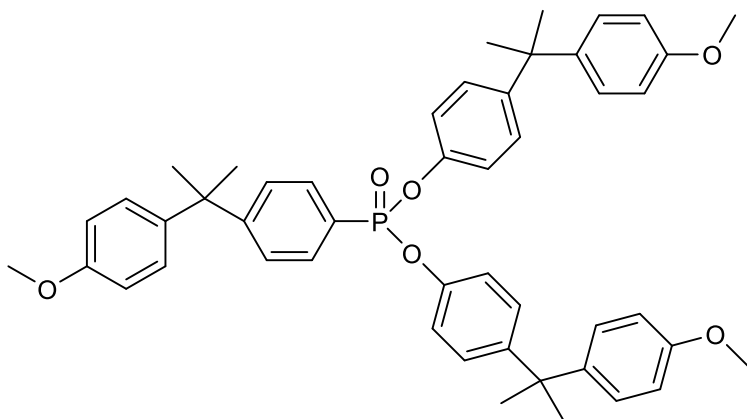
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.70 (d,  $J = 16.4$  Hz, 1H), 8.07-7.94 (m, 3H), 7.88 (d,  $J = 8.0$  Hz, 1H), 7.80-7.74 (m, 8H), 7.63-7.54 (m, 2H), 7.48-7.40 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.2 (d,  $J_{\text{C-P}} = 7.6$  Hz), 135.5, 135.4, 134.0, 132.4 (d,  $J_{\text{C-P}} = 17.4$  Hz), 131.1, 130.1, 129.3, 128.9, 128.8, 128.0, 127.8, 127.7, 127.3, 126.8, 126.5 (d,  $J_{\text{C-P}} = 9.9$  Hz), 125.7, 123.9 (d,  $J_{\text{C-P}} = 191.5$  Hz), 120.7 (d,  $J_{\text{C-P}} = 4.4$  Hz), 117.5 (d,  $J_{\text{C-P}} = 4.6$  Hz).  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.19. HRMS (ESI-TOF):  $m/z$ : ( $[\text{M}+\text{Na}]^+$ ) Calcd. for  $\text{C}_{30}\text{H}_{21}\text{NaO}_3\text{P}$  483.1126, Found 483.1127.



**Bis(4-(2-phenylpropan-2-yl)phenyl) (4-(2-phenylpropan-2-yl)phenyl)phosphonate (2v).**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.95 (dd,  $J = 8.4$  Hz, 13.6 Hz, 2H), 7.44 (dd,  $J = 4.4$  Hz, 8.4 Hz, 2H), 7.36-7.31 (m, 5H), 7.30-7.27 (m, 5H), 7.26-7.24 (m, 4H), 7.22 (d,  $J = 2.0$  Hz, 2H), 7.20 (s, 3H), 7.16-7.14 (m, 4H), 1.76 (s, 6H), 1.71 (s, 12H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.5 (d,  $J_{\text{C-P}} = 3.2$  Hz), 150.5, 149.7, 148.5 (d,  $J_{\text{C-P}} = 7.8$  Hz), 147.6, 132.2 (d,  $J_{\text{C-P}} = 10.8$  Hz), 128.4, 128.2, 128.2, 127.4, 127.2, 126.9, 126.2, 125.9, 124.5 (d,  $J_{\text{C-P}} = 195.5$  Hz), 120.2 (d,  $J_{\text{C-P}} = 4.3$  Hz), 43.6, 42.8, 31.0, 30.7.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.04. HRMS (ESI-TOF):  $m/z$ : ( $[\text{M}+\text{Na}]^+$ ) Calcd. for  $\text{C}_{45}\text{H}_{45}\text{NaO}_3\text{P}$  687.3004, Found 687.2995.





**Bis(4-(2-(4-methoxyphenyl)propan-2-yl)phenyl)**

**(4-(2-(4-methoxyphenyl)propan-2-**

**yl)phenyl)phosphonate (2w).**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.85 (dd,  $J = 7.6$  Hz, 13.6 Hz, 2H), 7.35 (dd,  $J = 4.4$  Hz, 7.6 Hz, 2H), 7.14-7.10 (m, 10H), 7.07-7.04 (m, 4H), 6.83-6.78 (m, 6H), 3.79 (s, 3H), 3.77 (s, 6H), 1.68 (s, 6H), 1.62 (s, 12H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  157.8, 157.6, 156.7 (d,  $J_{\text{C-P}} = 3.3$  Hz), 148.4 (d,  $J_{\text{C-P}} = 7.7$  Hz), 147.7, 142.6, 141.8, 132.1 (d,  $J_{\text{C-P}} = 10.9$  Hz), 128.1, 127.8, 127.8, 127.1 (d,  $J_{\text{C-P}} = 15.8$  Hz), 124.3 (d,  $J_{\text{C-P}} = 195.2$  Hz), 120.0 (d,  $J_{\text{C-P}} = 4.5$  Hz), 113.6, 113.4, 55.3, 42.8, 42.0, 31.1, 30.7.  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.92. HRMS (ESI-TOF):  $m/z$ : ( $[\text{M}+\text{Na}]^+$ ) Calcd. for  $\text{C}_{48}\text{H}_{51}\text{NaO}_6\text{P}$  777.3321, Found 777.3324.

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- [11] PdI(Ph)[P(OPh)<sub>3</sub>]<sub>2</sub> was known: Zawartka, W., Trzeciak, A. M., Ziolkowski, J. J., Lis, T., Ciunik, Z., Pernak,

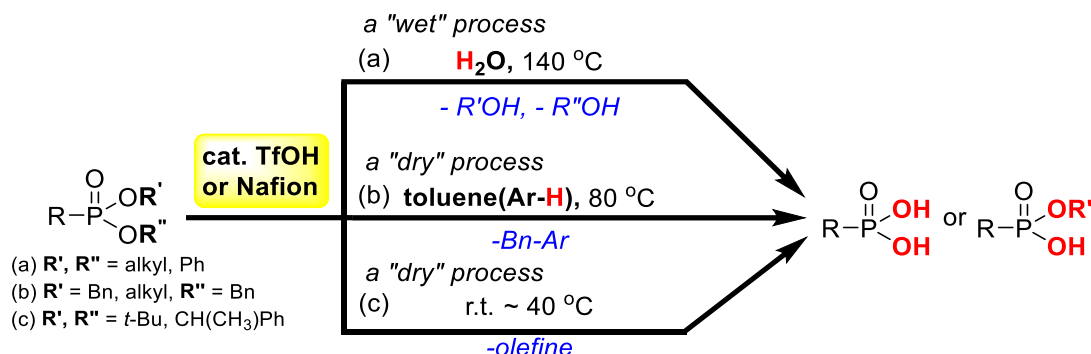
*J. Adv. Synth. Catal.* **2006**, 348, 1689.

## Chapter 4

# Brønsted Acid-Catalyzed Wet and Dry Processes for the Selective Transformation of Phosphonates to Phosphonic Acids

## Abstract

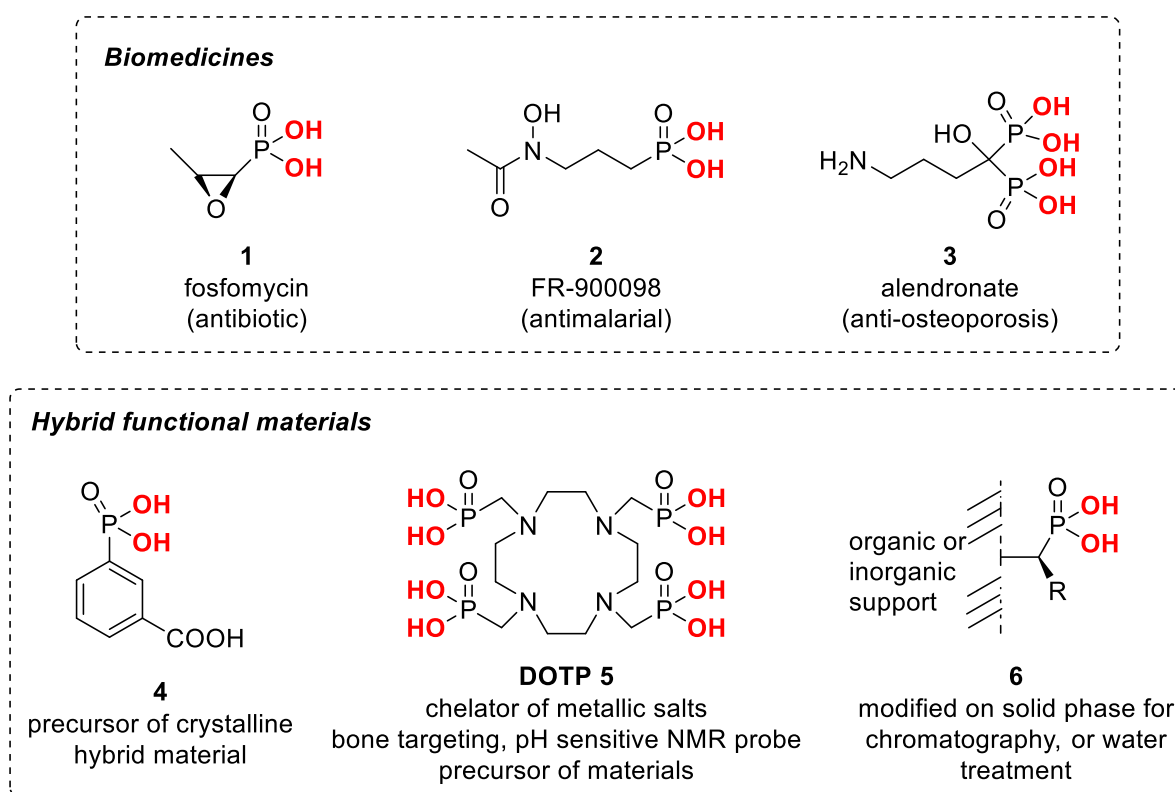
A “wet” process and two “dry” processes for converting phosphonate esters to phosphonic acids catalyzed by a Brønsted acid have been developed. Thus, in the presence of water, a range of alkyl, alkenyl and aryl substituted phosphonates can be generally hydrolyzed to the corresponding phosphonic acids in good yields catalyzed by trifluoromethyl sulfonic acid (TfOH) at 140 °C (the wet process). On the other hand, with specific substituents of the phosphonate esters, the conversion to the corresponding phosphonic acids can be achieved under milder conditions in the absence of water (the dry process). Thus, the conversion of dibenzyl phosphonates to the corresponding phosphonic acids took place smoothly at 80 °C in toluene or benzene in high yields. Moreover, a selective conversion of benzyl phosphonates  $\text{RP}(\text{O})(\text{OR}')(\text{OBn})$  to the corresponding mono phosphonic acids  $\text{RP}(\text{O})(\text{OR}')(\text{OH})$  can also be achieved under the reaction conditions. The dealkylation via the generation of isobutene of *di**tert*-butyl phosphonate and related catalyzed by TfOH took place even at room temperature to give the corresponding phosphonic acids in good to high yields. Nafion also shows high catalytic activity for these reactions. By using Nafion as the catalyst, phosphonic acids could be easily prepared in a large scale via a simple process.



## 4-1. Introduction

Phosphonic acids are an important class of compounds in medical and agricultural chemistry.<sup>1</sup> For examples, fosfomycin is a clinically used antibiotic, FR-900098 is an antimalarial, and alendronate is a widely employed anti-osteoporosis (Scheme 4-1).<sup>2a-2c</sup> These phosphonic acids are also widely used in the preparation of hybrid functional materials, as exemplified by compounds **4**, **DOTP 5** and **6** (Scheme 4-1).<sup>2d-2f</sup> Despite the importance, efficient and general methods for their synthesis are limited (Scheme 4-2).<sup>1a,3-8</sup>

**Scheme 4-1.** Selected examples of biomedicines and hybrid materials of phosphonic acids



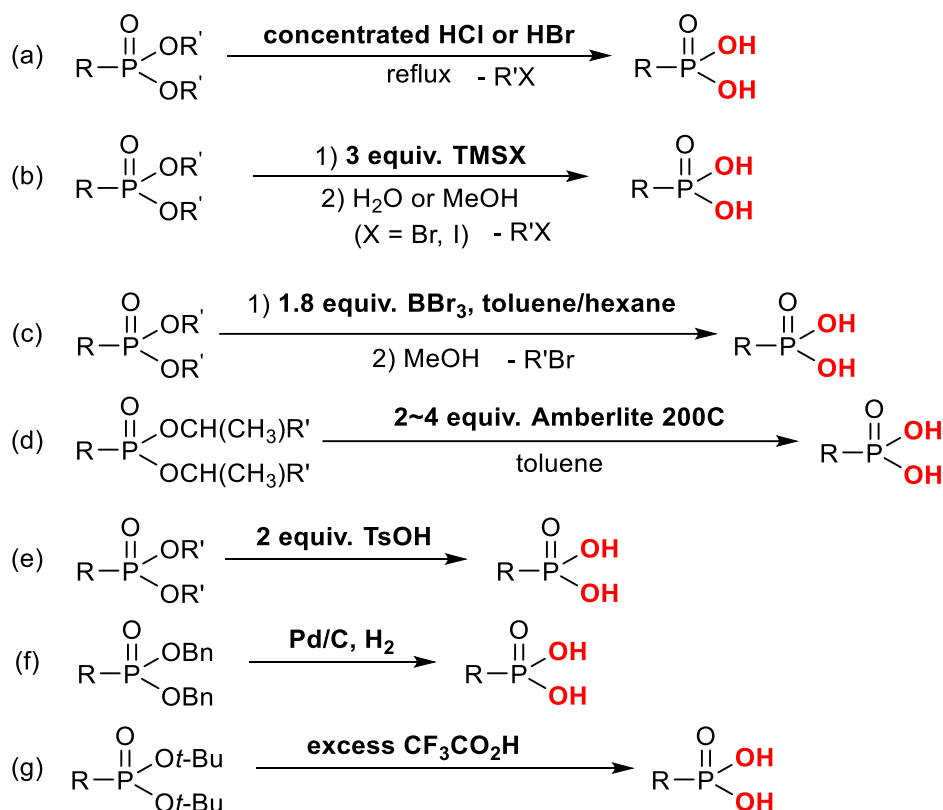
Currently, phosphonic acids are generally prepared via the hydrolysis of dialkyl phosphonates in hot concentrated hydrochloric acid (Scheme 4-2a)<sup>3</sup> or using halotrimethylsilanes (Scheme 4-2b).<sup>4</sup> However, the former requires a rather harsh reaction conditions and the later uses expensive halosilanes. Two equivalents of the toxic R'X were concomitantly generated from the reactions. In addition, the purification of the obtained phosphonic acids from the mixture was also a hard work. Dealkylation of dialkyl phosphonates could also be achieved by using BBr<sub>3</sub> (Scheme 4-2c).<sup>5</sup> Nitta et al reported the reaction of phosphonates with a cation-exchange resin (Amberlite 200C) (Scheme 4-2d)<sup>6a</sup> or TsOH (Scheme 4-2e)<sup>6b</sup> to prepare phosphonic acids.

However, all these reactions require an excess amount of  $\text{BBr}_3$ , cation exchange resin (Amberlite 200C) or TsOH. Hydrolysis by the palladium-catalyzed debenzylolation with hydrogen was also known (Scheme 4-2f).<sup>7</sup> However, the contamination of the heavy metal in the resulted phosphonic acids could be a problem. Ditert-butyl phosphonate was also used to prepare the corresponding phosphonic acid by treating it with a large excess amount of trifluoroacetic acid (Scheme 4-2g).<sup>8</sup>

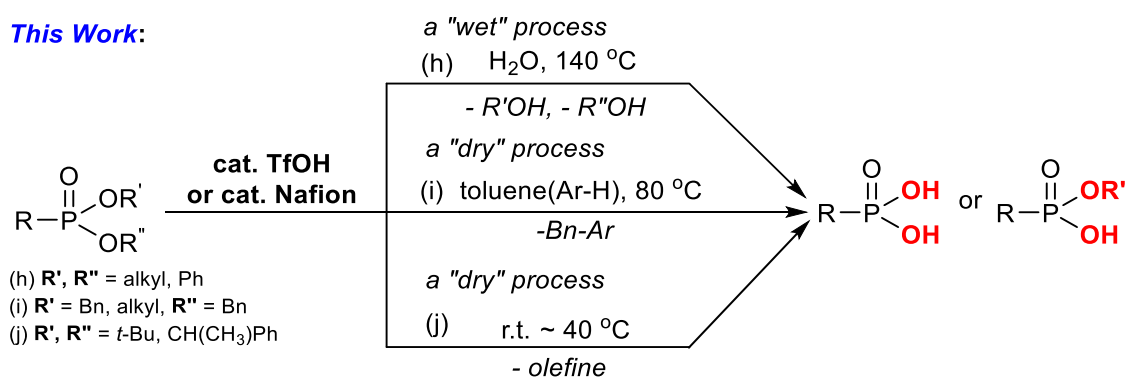
Herein, we report two catalytic ways for converting phosphonate esters to phosphonic acids, i.e. *the wet process*: a Brønsted acid TfOH can catalyze the hydrolysis of phosphonate esters to produce the corresponding phosphonic acids in good to high yields in the presence of water (Scheme 4-2h), and *the dry process*: in the absence of water, benzyl phosphonates can be converted to the corresponding phosphonic acids under mild conditions in toluene (Scheme 4-2i). In addition, monosubstituted phosphonic acids could be selectively obtained by using this dry process from the corresponding benzyl phosphonates (Scheme 4-2i). Moreover, *tert*-butyl phosphonates and related can readily give the corresponding phosphonic acids even at room temperature (Scheme 4-2j). The recyclable solid acid Nafion also shows high catalytic activity for these reactions. By using Nafion as the catalyst, phosphonic acids can be easily prepared from the corresponding phosphonate esters in gram-scale reaction via a simple process.

#### **Scheme 4-2.** Synthesis of phosphonic acids

### Traditional Methods:



### This Work:



## 4-2. The "Wet" Process for Converting Phosphonate Esters to Phosphonic Acids

### 4-2-1. Optimization of Reaction Conditions

As an extension of our study on the selective cleavage of C–O and P–O bonds of phosphites (RO)<sub>3</sub>P catalyzed by a Brønsted acid,<sup>9</sup> we found that TfOH was able to catalyze the C–O cleavage of dimethyl vinylphosphonate (**1a**) to generate the corresponding vinylphosphonic acid in the presence of water. As shown in Table 4-1, 92% yield of **2a** was obtained by heating a mixture of **1a** and water in the presence of 10 mol% H<sub>3</sub>PO<sub>3</sub> (Table 4-1, entry 1). Only 27% yield of **2a** was formed under similar reaction conditions without the

acid (Table 4-1, entry 2). When **1a** was treated with a perfluorinated sulfonic acid (TfOH) under similar conditions, the yield of **2a** increased to 96% (Table 4-1, entry 3). The yield of **2a** reduced to 52% when the reaction was conducted at 120 °C (Table 4-1, entry 4). This reaction also took place smoothly by using only 2 equivs water (Table 4-1, entry 5). Under similar reaction conditions, **1a** was heated at 140 °C for 8 h and 16 h to produce **2a** in 65% and 93% yield, respectively (Table 4-1, entries 6 and 7). Practically importantly, a solid acid Nafion<sup>10</sup> is equally active as the catalyst, affording almost a quantitative yield of **2a** under similar reaction conditions (Table 4-1, entry 8). As described below, the use of Nafion catalyst can dramatically simplify the preparation process of phosphonic acids since unlike the difficult removal of TfOH from the products<sup>8a</sup> Nafion can be easily separated from the products by a simple filtration.<sup>10</sup>

**Table 4-1.** A Brønsted acid-catalyzed hydrolysis of **1a**<sup>a</sup>

entry	cat.	H <sub>2</sub> O	temperature/°C	time	yield <sup>b</sup> ( <b>2a</b> )
1	H <sub>3</sub> PO <sub>3</sub>	0.2 mL	140	24 h	92%
2	none	0.2 mL	140	24 h	27%
3	TfOH	0.2 mL	140	24 h	96%
4	TfOH	0.2 mL	120	24 h	52%
5	TfOH	2 equiv.	140	24 h	88%
6	TfOH	0.2 mL	140	8 h	65%
7	TfOH	0.2 mL	140	16 h	93%
8 <sup>c</sup>	Nafion	0.2 mL	140	24 h	95%

<sup>a</sup>Reaction conditions: a mixture of **1a** (2.53 mmol), catalyst (10 mol%) and H<sub>2</sub>O was heated for 24 h in a 10 mL sealed glass tube.

<sup>b</sup>Yields based on <sup>31</sup>P NMR analysis. <sup>c</sup>10 mg was used.

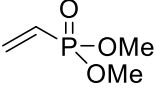
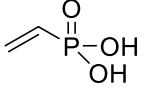
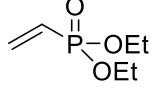
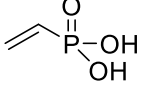
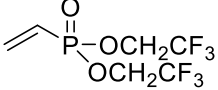
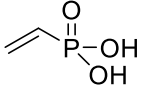
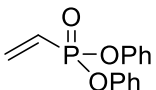
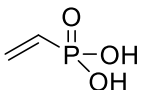
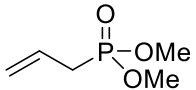
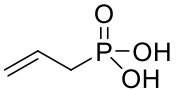
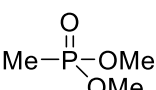
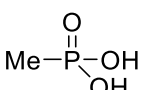
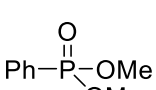
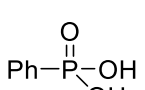
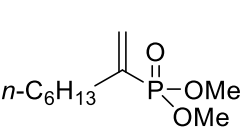
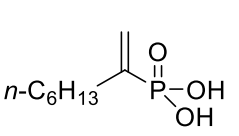
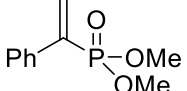
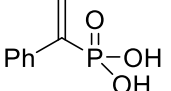
#### 4-2-2. Scope of Substrates

This hydrolysis reaction was rather general for the synthesis of phosphonic acids. A variety of phosphonate



esters under the present reaction conditions gave the corresponding phosphonic acids **2** in good to excellent yields. As shown in Table 4-2, compared to dimethyl vinylphosphonate **1a**, the hydrolysis of diethyl vinylphosphonate **1b** (Table 4-2, entry 2) was slow and 76% yield of vinylphosphonic acid was obtained after 48 h heating. In contrast, bis(2,2,2-trifluoroethyl) vinylphosphonate **1c** readily produced vinylphosphonic acid **2a** in 96% yield (Table 4-2, entry 3). Therefore, an electron-deficient group fastens the hydrolysis. Similarly, diphenyl vinylphosphonate **1d** (Table 4-2, entry 4) was also readily hydrolyzed to give a high yield of vinylphosphonic acid **2a** under the standard conditions. Under similar conditions, allylphosphonic acid **2e** was obtained in 89% yield by the hydrolysis of the corresponding dimethyl allylphosphonate **1e** (Table 4-2, entry 5). Methylphosphonic acid **2f** and phenylphosphonic acid **2g** were also obtained from the hydrolysis of the corresponding dimethyl phosphonates **1f** and **1g**, in high yields (Table 4-2, entries 6 and 7), respectively. Similarly, the hydrolysis of dimethyl 1-octen-2-yl-phosphonate **1h** and dimethyl (1-phenylvinyl)phosphonate **1i** (Table 4-2, entries 8 and 9) produced good yields of the corresponding phosphonic acids **2h** and **2i**, respectively.

**Table 4-2.** Hydrolysis of phosphonate esters catalyzed by TfOH<sup>a</sup>

$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{R}-\text{P}-\text{OR}' \\  \parallel \\  \text{OR}' \\  \mathbf{1}  \end{array}  \xrightarrow[140\text{ }^{\circ}\text{C, 24 h}]{10\text{ mol\% TfOH, H}_2\text{O}}  \begin{array}{c}  \text{O} \\  \parallel \\  \text{R}-\text{P}-\text{OH} \\  \parallel \\  \text{OH} \\  \mathbf{2}  \end{array}  $				
entry	substrate <b>1</b>		product <b>2</b> (isolated yield)	
1	 <b>1a</b>		 <b>2a</b> , 91%	
2 <sup>b</sup>	 <b>1b</b>		 <b>2a</b> , 76%	
3	 <b>1c</b>		 <b>2a</b> , 96%	
4	 <b>1d</b>		 <b>2a</b> , 95%	
5	 <b>1e</b>		 <b>2e</b> , 89%	
6	 <b>1f</b>		 <b>2f</b> , 93%	
7 <sup>b</sup>	 <b>1g</b>		 <b>2g</b> , 90%	
8	 <b>1h</b>		 <b>2h</b> , 54%	
9	 <b>1i</b>		 <b>2i</b> , 81%	

<sup>a</sup>Reaction conditions: a mixture of **1** (2.53 mmol), 10 mol% TfOH and 0.2 mL H<sub>2</sub>O was heated under air in a 10 mL sealed glass tube at 140 °C for 24 h. <sup>b</sup>48 h.

### 4-3. “Dry” Processes for Converting Phosphonate Esters to Phosphonic Acids (with toluene)

#### 4-3-1. Optimization of Reaction Conditions

As described above, the wet process by the hydrolysis of phosphonates with water catalyzed by a Brønsted acid could give the corresponding phosphonic acids. However, a long-time heating at a high temperature (140 °C) was necessary. In addition, the removal of water from the products under vacuum also takes a long time.

Therefore, a more efficient process for converting phosphonate esters to phosphonic acids under *dry and mild conditions* is desirable. Fortunately, we could solve this problem. Thus, to our delight, we found that, *in the absence of water*, by simply heating dibenzyl phenylphosphonate **1j** in benzene or toluene at 80 °C in the presence of a catalytic amount of TfOH, the debenzylation took place efficiently to produce the corresponding phosphonic acid **2g** in high yields (Table 4-3). For example, in the presence of 10 mol% TfOH, **1j** was heated in toluene at 80 °C for 4 h and 6 h to produce **2g** in 25% and 54% yield, respectively. (Table 4-3, entries 1 and 2).<sup>11</sup> When the reaction time was extended to 8 h, a quantitative yield of **2g** was obtained (Table 4-3, entry 3). However, only 8% and 2% yields of **2g** were obtained when the reactions were performed at 60 °C and 40 °C, respectively (Table 4-3, entries 4 and 5). The debenzylation took place slowly in benzene, and 35% and 68% yields of **2g** were obtained at 80 °C in 8 h and 12 h, respectively (Table 4-3, entries 6 and 7). When the reaction time was extended to 16 h, a quantitative yield of **2g** was also produced (Table 4-3, entry 8). In CH<sub>2</sub>Cl<sub>2</sub>, only a trace amount of product was detected (Table 4-3, entry 9). For comparison, **2g** could not be observed at all in water (Table 4-3, entry 10). No reaction took place in the absence of the acid catalyst (Table 4-3, entry 11) or with H<sub>3</sub>PO<sub>3</sub> (Table 4-3, entry 12), showing the exceptional catalytic reactivity of the perfluorinated sulfonic acids for this reaction. Solid Nafion was also active for this reaction, and gave a quantitative yield of **2g** under similar reaction conditions (Table 4-3, entry 13).

**Table 4-3.** A Brønsted acid-catalyzed debenzylation of **1j**<sup>a</sup>

$  \begin{array}{ccc}  \text{O} & & \text{O} \\     & &    \\  \text{Ph}-\text{P}-\text{OBn} & \xrightarrow{\text{cat., solvent}} & \text{Ph}-\text{P}-\text{OH} \\    & &   \\  \text{OBn} & & \text{OH} \\  \mathbf{1j} & & \mathbf{2g}  \end{array}  $					
entry	cat.	solvent	temperature/°C	time	yield <sup>b</sup> ( <b>2g</b> )
1	TfOH	toluene	80	4 h	25%
2	TfOH	toluene	80	6 h	54%
3	TfOH	toluene	80	8 h	>99%
4	TfOH	toluene	60	8 h	8%

5	TfOH	toluene	40	8 h	2%
6	TfOH	benzene	80	8 h	35%
7	TfOH	benzene	80	12 h	68%
8	TfOH	benzene	80	16 h	>99%
9	TfOH	CH <sub>2</sub> Cl <sub>2</sub>	80	8 h	trace
10	TfOH	H <sub>2</sub> O	80	8 h	N.D.
11	none	toluene	80	8 h	N.D.
12	H <sub>3</sub> PO <sub>3</sub>	toluene	80	8 h	N.D.
13 <sup>c</sup>	Nafion	toluene	80	8 h	>99%

<sup>a</sup>Reaction conditions: a mixture of **1j** (0.5 mmol) and a catalyst (10 mol%) in a solvent (1 mL) was heated in a 10 mL sealed glass tube. <sup>b</sup>Yields based on <sup>31</sup>P NMR analysis dissolved in methanol. <sup>c</sup>10 mg was used.

#### 4-3-2. Scope of Substrates

This efficient debenzylation reaction could be applied to other substrates. As shown in Table 4, dibenzyl vinylphosphonate **1k** and octylphosphonate **1l** also gave the corresponding vinylphosphonic acid **2a** and octylphosphonic acid **2l** in 93% and 95% yield, respectively, under similar conditions (Table 4-4, entries 2 and 3). Similarly, diallyl phenylphosphonate produced phenylphosphonic acid **2g** in 75% yield (Table 4-4, entry 4). However, phenylphosphonic acid **2g** was not formed at all from dimethyl phenylphosphonate (Table 4-4, entry 5) under this water-free condition. This novel difference in reactivity between methyl and benzyl groups makes the generation of monosubstituted phosphonic acids possible via selective dealkylation of phosphonates and related. For example, the benzyl group was selectively removed from benzylmethyl phenylphosphonate **1n** to produce methyl phenylphosphonic acid **2n** in 82% yield (Table 4-4, entry 6). Similarly, benzyldiethyl phosphate and dibenzylethyl phosphate were selectively debenzylated to selectively produce the disubstituted phosphoric acid diethyl phosphoric acid **2o** and monosubstituted phosphoric acid monoethyl phosphoric acid **2p** in 93% and 94% yield, respectively (Table 4-4, entries 7 and 8). Note that a selective synthesis of these phosphoric acid derivatives is rather difficult and required complicated manipulations.

**Table 4-4.** Selective generation of phosphonic acids by debenzylation of benzyl phosphonates and related

catalyzed by TfOH<sup>a</sup>

$\text{R}-\text{P}(\text{O})(\text{OR}')(\text{OR}'') \xrightarrow[80\text{ }^{\circ}\text{C}, 8\text{ h}]{10\text{ mol\% TfOH, toluene}} \text{R}-\text{P}(\text{O})(\text{OH})_2$				
<b>1</b>			<b>2</b>	
entry	substrate <b>1</b>		product <b>2</b> (isolated yield)	
1	$\text{Ph}-\text{P}(\text{O})(\text{OBn})_2$	<b>1j</b>	$\text{Ph}-\text{P}(\text{O})(\text{OH})_2$	<b>2g</b> , 90%
2	$\text{CH}_2=\text{CH}-\text{P}(\text{O})(\text{OBn})_2$	<b>1k</b>	$\text{CH}_2=\text{CH}-\text{P}(\text{O})(\text{OH})_2$	<b>2a</b> , 93%
3 <sup>b</sup>	$n\text{-C}_8\text{H}_{17}-\text{P}(\text{O})(\text{OBn})_2$	<b>1l</b>	$n\text{-C}_8\text{H}_{17}-\text{P}(\text{O})(\text{OH})_2$	<b>2l</b> , 95%
4 <sup>c</sup>	$\text{Ph}-\text{P}(\text{O})(\text{Oallyl})_2$	<b>1m</b>	$\text{Ph}-\text{P}(\text{O})(\text{OH})_2$	<b>2g</b> , 75%
5	$\text{Ph}-\text{P}(\text{O})(\text{OMe})_2$	<b>1g</b>	$\text{Ph}-\text{P}(\text{O})(\text{OH})_2$	<b>2g</b> , N.D
6	$\text{Ph}-\text{P}(\text{O})(\text{OBn})(\text{MeO})$	<b>1n</b>	$\text{Ph}-\text{P}(\text{O})(\text{OH})(\text{MeO})$	<b>2n</b> , 82%
7	$\text{EtO}-\text{P}(\text{O})(\text{OBn})(\text{EtO})$	<b>1o</b>	$\text{EtO}-\text{P}(\text{O})(\text{OH})(\text{EtO})$	<b>2o</b> , 93%
8	$\text{EtO}-\text{P}(\text{O})(\text{OBn})_2$	<b>1p</b>	$\text{EtO}-\text{P}(\text{O})(\text{OH})_2$	<b>2p</b> , 94%

<sup>a</sup>Reaction conditions: a mixture of **1** (0.5 mmol), 10 mol% TfOH and 1 mL toluene was heated in a 10 mL sealed glass tube at 80 °C for 8 h. <sup>b</sup>100 °C, 24 h. <sup>c</sup>120 °C, 24 h.

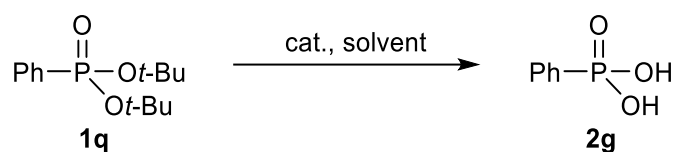
## 4-4. “Dry” Processes for Converting Phosphonate Esters to Phosphonic Acids (-alkene)

### 4-4-1. Optimization of Reaction Conditions

Worth noting is that, when the benzyl group was replaced by *tert*-butyl, the reaction could take place at room temperature to give almost a quantitative yield of the corresponding phosphonic acid **2g** (Table 4-5). For example, in the presence of 10 mol% TfOH, **1q** was heated in toluene at 80 °C or 60 °C for 30 minutes to

produce **2g** in quantitative yield (Table 4-5, entries 1 and 2). A quantitative yield of **2g** was also obtained by carrying out the reaction at 40 °C for 2 h or at room temperature for 5 h (Table 4-5, entries 3 and 4). Similarly, the dealkylation also took place in benzene or CH<sub>2</sub>Cl<sub>2</sub> to give **2g** in 92% and 90% yield, respectively (Table 4-5, entries 5 and 6). It was noted that no reaction took place in the absence of the acid (Table 4-5, entry 7) or with H<sub>3</sub>PO<sub>3</sub> (Table 4-5, entry 8), showing the exceptional catalytic reactivity of the perfluorinated sulfonic acids for this reaction. Solid Nafion was also active for this reaction, and gave a quantitative yield of **2g** under similar reaction conditions (Table 4-5, entry 9).

**Table 4-5.** A Brønsted acid-catalyzed *tert*-butylation of **1q**<sup>a</sup>



entry	cat.	solvent	temperature/°C	time	yield <sup>b</sup> ( <b>2g</b> )
1	TfOH	toluene	80	30 min	>99%
2	TfOH	toluene	60	30 min	>99%
3	TfOH	toluene	40	2 h	>99%
4	TfOH	toluene	r.t.	5 h	>99%
5	TfOH	benzene	r.t.	5 h	92%
6	TfOH	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	5 h	90%
7	none	toluene	r.t.	5 h	N.D.
8	H <sub>3</sub> PO <sub>3</sub>	toluene	r.t.	5 h	N.D.
9 <sup>c</sup>	Nafion	toluene	r.t.	8 h	>99%

<sup>a</sup>Reaction conditions: a mixture of **1q** (0.5 mmol) and a catalyst (10 mol%) in a solvent (1 mL) was heated in a 10 mL sealed glass tube. <sup>b</sup>Yields based on <sup>31</sup>P NMR analysis dissolved in methanol. <sup>c</sup>10 mg was used.

#### 4-4-2. Scope of Substrates

This efficient dealkylation reaction could also be applied to other *sec*-alkyl substituent phosphonates. As shown in Table 4-6, di(1-phenylethyl) phenylphosphonate **1r** also gave the corresponding phenylphosphonic

acid **2g** in 94% yield under similar conditions (Table 4-6, entry 2). Moreover, diisopropyl phenylphosphonate **1s** also produced phenylphosphonic acid **2g** in 92% yield under similar conditions, though a higher temperature was required (Table 4-6, entry 3). Similarly, diisopropyl vinylphosphonate and octylphosphonate were deisopropylated to produce the corresponding vinylphosphonic acid **2a** and octylphosphonic acid **2l** in 92% and 61% yield, respectively (Table 4-6, entries 4 and 5).

**Table 4-6.** Generation of phosphonic acids by dealkylation catalyzed by TfOH<sup>a</sup>

$\text{R}-\text{P}(\text{O})(\text{OR}')_2 \xrightarrow[40\text{ }^\circ\text{C, 2 h}]{10\text{ mol\% TfOH, toluene}} \text{R}-\text{P}(\text{O})(\text{OH})_2$		
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <math>\text{1}</math> </div> <div style="text-align: center;"> <math>\text{2}</math> </div> </div>		
entry	substrate <b>1</b>	product <b>2</b> (isolated yield)
1	$\text{Ph}-\text{P}(\text{O})(\text{O}t\text{-Bu})_2$ <b>1q</b>	$\text{Ph}-\text{P}(\text{O})(\text{OH})_2$ <b>2g</b> , 95%
2	$\text{Ph}-\text{P}(\text{O})(\text{OCH}(\text{CH}_3)\text{Ph})_2$ <b>1r</b>	$\text{Ph}-\text{P}(\text{O})(\text{OH})_2$ <b>2g</b> , 94%
3 <sup>b</sup>	$\text{Ph}-\text{P}(\text{O})(\text{O}i\text{-Pr})_2$ <b>1s</b>	$\text{Ph}-\text{P}(\text{O})(\text{OH})_2$ <b>2g</b> , 92%
4 <sup>b</sup>	$\text{CH}_2=\text{CH}-\text{P}(\text{O})(\text{O}i\text{-Pr})_2$ <b>1t</b>	$\text{CH}_2=\text{CH}-\text{P}(\text{O})(\text{OH})_2$ <b>2a</b> , 92%
5 <sup>c</sup>	$n\text{-C}_8\text{H}_{17}-\text{P}(\text{O})(\text{O}i\text{-Pr})_2$ <b>1u</b>	$n\text{-C}_8\text{H}_{17}-\text{P}(\text{O})(\text{OH})_2$ <b>2l</b> , 61%

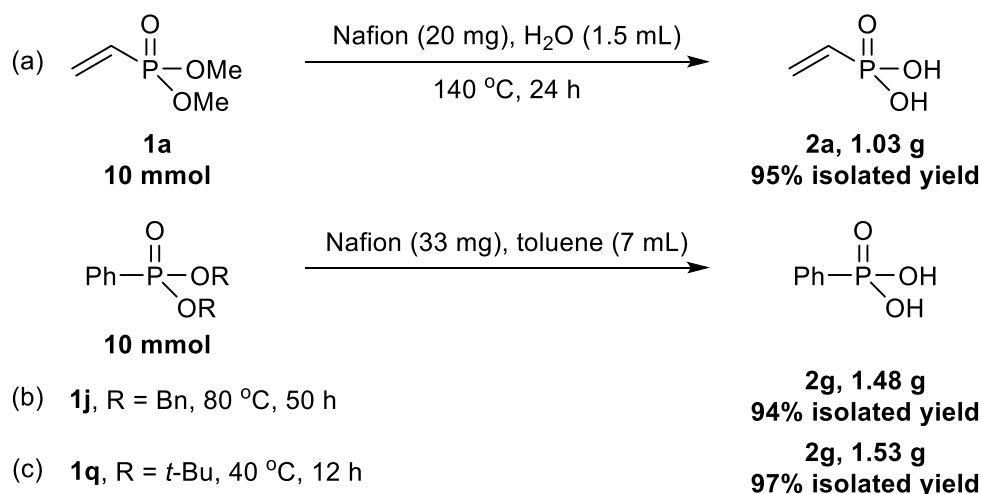
<sup>a</sup>Reaction conditions: a mixture of **1** (0.5 mmol), 10 mol% TfOH and 1 mL toluene was heated in a 10 mL sealed glass tube at 40 °C for 2 h. <sup>b</sup>120 °C, 24 h. <sup>c</sup>120 °C, 50 h.

## 4-5. The Recoverable and Reusable Solid Nafion as the Catalyst

The advantages of the present methods compared to the old ones are apparent as demonstrated in Scheme 4-3.<sup>10</sup> As shown in Scheme 4-3a, a trace amount of Nafion catalyst effectively catalyzed the conversion of **1a** to **2a** in a 10 mmol scale reaction of dimethyl vinylphosphonate **1a** with water. After the reaction, a simple filtration removing the solid catalyst Nafion followed by evaporation of the solution under vacuum could give

highly pure vinylphosphonic acid in a high yield. Similarly, as shown in Scheme 4-3b and 4-3c, all the reactions are very efficient for the conversion of **1j** and **1q**, to give the corresponding phosphonic acid **2g** in 94% and 97% isolated yields, respectively, by simply removing the solid catalyst via filtration.

**Scheme 4-3.** 10 mmol-scale reactions using solid acid Nafion as the catalyst



## 4-6. Mechanistic Studies

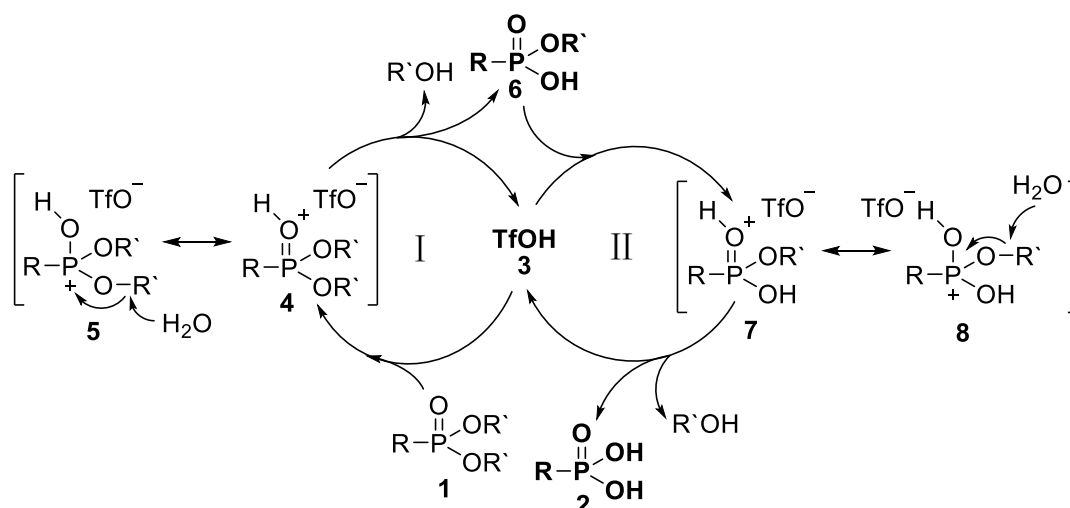
On the bases of the literatures reported,<sup>12,13</sup> a plausible mechanism of the hydrolysis of dialkyl phosphonates catalyzed by Brønsted acid in water was proposed (Scheme 4-4). Firstly, TfOH may protonize dialkyl phosphonate **1** to give the intermediate **4** which was transformed to phosphonium salt **5**. Phosphonium salt **5** may undergo C–O cleavage via a S<sub>N</sub>2-type attack of H<sub>2</sub>O at the R' group of **5** to give intermediate **6**, R'OH, and regenerate TfOH, as TfO<sup>−</sup> is a weak nucleophile.<sup>14</sup> On the one hand, the regenerated TfOH may then protonize **6** to give the **7** and **8**. Subsequently, phosphonium salt **8** reacts with water to produce **2**, R'OH, and regenerate TfOH.

It should be noted that the above S<sub>N</sub>2-type C–O bond cleavage mechanism might not be applicable to diphenyl phosphonates RP(O)(OPh)<sub>2</sub>. Alternatively, a P–O bond cleavage, rather than an O–Ph bond cleavage, might take place in cases of RP(O)(OPh)<sub>2</sub>.<sup>1a</sup>

**Scheme 4-4.** A proposed mechanism of the hydrolysis of dialkyl phosphonates catalyzed by a Brønsted acid

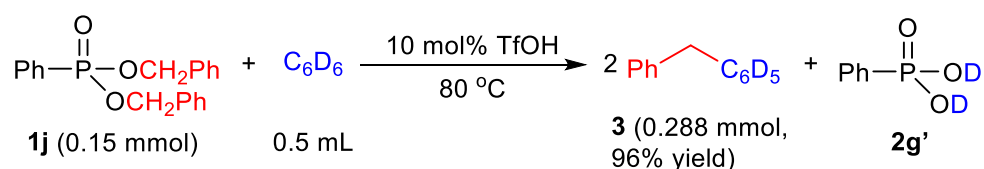


in water



On the other hand, to probe the debenzylation reaction mechanism in toluene or benzene, control reactions were conducted (Scheme 4-5). When dibenzyl phenylphosphonate **1j** was allowed to debenzylate in benzene- $d_6$  catalyzed by TfOH under the standard reaction conditions, **3** having a  $C_6D_5$  unit was produced in almost a quantitative yield as determined by  $^1H$  NMR spectroscopy using 1,4-dioxane as an internal standard, indicating that the reaction took place as shown in Scheme 5.<sup>15</sup>

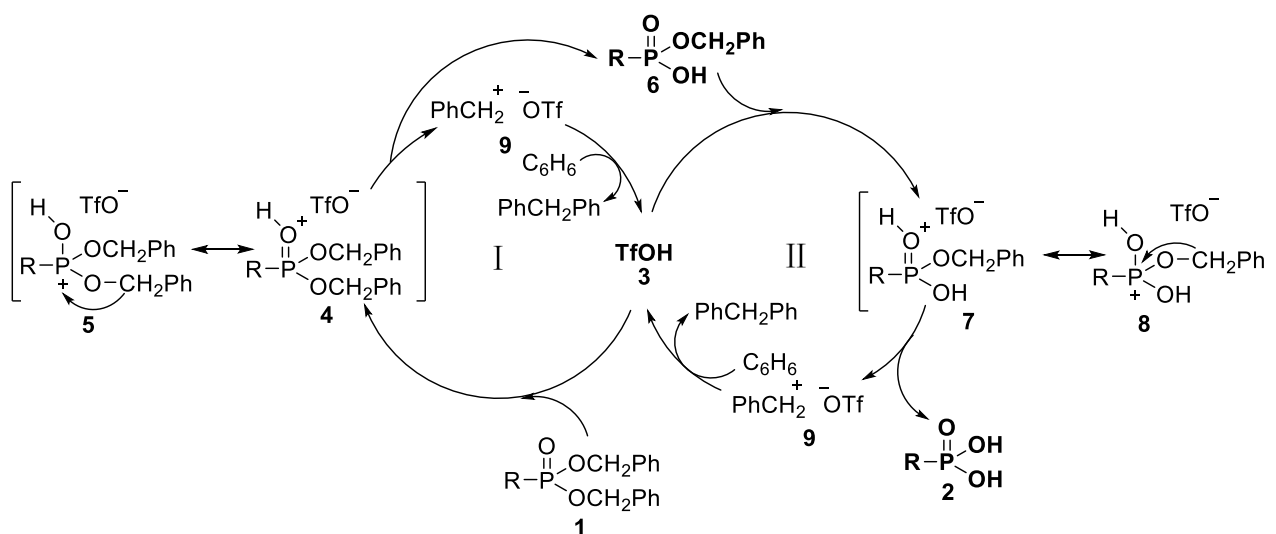
**Scheme 4-5.** The reaction of dibenzyl phenylphosphonate (**1j**) with benzene- $d_6$  catalyzed by TfOH



The mechanism is not fully understood at present. A plausible mechanism of the debenzylation of dibenzyl phosphonates catalyzed by a Brønsted acid in benzene was shown in Scheme 4-6.<sup>6,11</sup> TfOH may firstly protonize dibenzyl phosphonate **1** to give the intermediate **4** which could be transformed to phosphonium salt **5**. Phosphonium salt **5** may directly decompose undergo C–O cleavage via a  $S_N1$ -type mechanism to give **9** and intermediate **6**. Then **9** reacts with benzene to give diphenylmethane that could be detected by GC-MS<sup>16</sup> and regenerates TfOH. The regenerated TfOH then should further react with **6** to produce **2**.

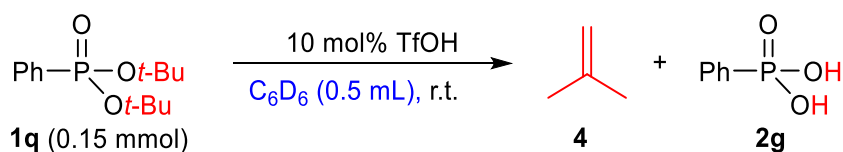
**Scheme 4-6.** A proposed mechanism of the debenzylation of dibenzyl phosphonate (**1j**) catalyzed by

## Brønsted acid in benzene



The *detert*-butylation reaction was considered as a similar reaction with the well-employed regeneration of an alcohol ROH from *t*-BuOR by the deprotection of the *tert*-butyl group.<sup>17</sup> Indeed, when ditert-butyl phenylphosphonate **1q** was allowed to react in benzene-*d*<sub>6</sub> in the presence of TfOH under the standard reaction conditions, isobutene **4** was generated as confirmed by <sup>1</sup>H NMR spectroscopy (Scheme 4-7).

**Scheme 4-7.** The *detert*-butylation of ditert-butyl phenylphosphonate (**1q**) in benzene-*d*<sub>6</sub> catalyzed by TfOH



## 4-7. Conclusions

In summary, we have developed a wet and two dry methods to prepare phosphonic acids from phosphonate esters catalyzed by Brønsted acids. A variety of phosphonates could be efficiently protonated in water or, in the absence of water, in toluene and benzene. Furthermore, selective monodealkylation of dialkyl phosphonates could be achieved by employing this Brønsted acid-catalyzed method in toluene under mild

conditions. The reusable solid acid Nafion could be used as the catalyst for these reactions, that made the preparation of phosphonic acids simple and easy.

## 4-8. Experimental Section

### 4-8-1. General Information

In summary, we have developed a wet and two dry methods to prepare phosphonic acids from phosphonate esters catalyzed by Brønsted acids. A variety of phosphonates could be efficiently protonated in water or, in the absence of water, in toluene and benzene. Furthermore, selective monodealkylation of dialkyl phosphonates could be achieved by employing this Brønsted acid-catalyzed method in toluene under mild conditions. The reusable solid acid Nafion could be used as the catalyst for these reactions, that made the preparation of phosphonic acids simple and easy.

Unless otherwise noted, reactions with water were carried out in Schlenk tubes under air atmosphere, and reactions with toluene were carried out in oven-dried Schlenk tubes under Ar atmosphere. All reagents were purchased and used as received. Phosphonate esters were either purchased or prepared from the corresponding alcohols and phosphorochloridate according to literature procedures.<sup>6a</sup> Mass spectra were recorded at Shimadzu GCMS-QP 2010 plus spectrometer. Flash column chromatography was performed using 200-300 mesh silica gel. <sup>1</sup>H, <sup>13</sup>C, <sup>31</sup>P and <sup>19</sup>F NMR were recorded on a JEOL JNM-ECS400 (400 MHz for <sup>1</sup>H, 100 MHz for <sup>13</sup>C, 162 MHz for <sup>31</sup>P and 377 MHz for <sup>19</sup>F spectroscopy). Chemical shifts for <sup>1</sup>H NMR are referred to internal Me<sub>4</sub>Si (0 ppm) and reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Chemical shifts for <sup>31</sup>P NMR were relative to H<sub>3</sub>PO<sub>4</sub> (85% solution in D<sub>2</sub>O, 0 ppm).

### 4-8-2. Typical procedure for TfOH-catalyzed hydrolysis of phosphonate esters in H<sub>2</sub>O

To a 10 mL Schlenk tube in air was added dimethyl vinylphosphonate **1a** (0.59 mL, 5 mmol), H<sub>2</sub>O (0.4 mL) and trifluoromethanesulfonic acid (44.2 μL, 10 mol%). The tube was heated at 140 °C using a heating aluminum block for 24 h and **1a** was consumed as confirmed by <sup>31</sup>P NMR spectroscopy. After removal of the volatiles, the residues (light brown oil) were purified by passing through a short silica gel column (200-300 mesh, dichloromethane/methanol = 4:1 as eluent) to obtain pure product **2a** (colorless oil) in 91% isolated

yield (491.5 mg) after removing the volatiles under vacuum (ca 20 Pa) at 130 °C overnight.

#### **4-8-3. 10 mmol-Scale hydrolysis of dimethyl vinylphosphonate with H<sub>2</sub>O using Nafion as catalyst**

To a 10 mL Schlenk tube was added dimethyl vinylphosphonate **1a** (1.19 mL, 10 mmol), H<sub>2</sub>O (1.5 mL) and Nafion (20 mg). The tube was then heated at 140 °C for 24 h. Pure **2a** was obtained after filtration removing Nafion and evaporation under vacuum removing volatiles in 95% isolated yield (1.03 g).

#### **4-8-4. A typical procedure for TfOH-catalyzed debenzylation of phosphonates in toluene**

To a 10 mL Schlenk tube was added dibenzyl phenylphosphonate **1j** (676.8 mg, 2 mmol), trifluoromethanesulfonic acid (17.7 µL, 10 mol%) and toluene (2 mL) under Ar. The tube was then heated at 80 °C for 24 h. The product precipitated as a light brown solid. After removal of the liquids, the residues (light brown solid) were purified by passing through a short silica gel column (200-300 mesh, dichloromethane/methanol = 3:1) to obtain **2g** (white solid) in 91% isolated yield after drying under vacuum (287.8 mg).

#### **4-8-5. 10 mmol-Scale debenzylation of phosphonates in toluene using Nafion as catalyst**

To a 25 mL Schlenk tube was added dibenzyl phenylphosphonate **1j** (3.4 g, 10 mmol), Nafion (33 mg) and toluene (7 mL) under Ar. The tube was then heated at 80 °C for 50 h. Water was added to dissolve the product precipitated out and then Nafion was removed by filtration. The aqua solution was collected and volatiles were pumped off under vacuum to give pure **2g** as a white solid in 94% isolated yield (1.48 g).

#### **4-8-6. A typical procedure for TfOH-catalyzed *tert*-butylation of phosphonates in toluene**

To a 10 mL Schlenk tube was added *tert*-butyl phenylphosphonate **1q** (540.6 mg, 2 mmol), trifluoromethanesulfonic acid (17.7 µL, 10 mol%) and toluene (2 mL) under Ar. The tube was then heated at 40 °C for 2 h and **1q** was completely consumed. The product precipitated out as a light brown solid. After removal of the liquid mixture, the residues (light brown solid) were purified by passing through a short silica gel column (200-300 mesh, dichloromethane/methanol = 3:1 as eluent) to obtain pure product **2g** in 92% isolated yield (white solid, 290.9 mg).

#### **4-8-7. 10 mmol-Scale *tert*-butylation of phosphonates in toluene catalyzed by Nafion**

To a 25 mL Schlenk tube was added *tert*-butyl phenylphosphonate **1q** (2.7 g, 10 mmol), Nafion (33 mg)

and toluene (7 mL) under Ar. The tube was then heated at 40 °C for 12 h. The product precipitated as a white solid. 7 mL MeOH was added to dissolve the white solid. Pure **2g** was obtained after filtration removing Nafion and pumping off the volatiles under vacuum in 97% isolated yield (white solid, 1.53 g).

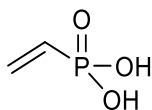
#### 4-8-8. The reaction of dibenzyl phenylphosphonate (**1j**) in benzene-*d*<sub>6</sub> catalyzed by TfOH

To an NMR tube was added dibenzyl phenylphosphonate **1j** (50.8 mg, 0.15 mmol) and C<sub>6</sub>D<sub>6</sub> (0.5 mL), and its <sup>1</sup>H NMR was taken. Trifluoromethanesulfonic acid (1.3 μL, 10 mol%) was then added to the NMR tube. The tube was gently shaken at room temperature for ca. 0.5 h, and was subjected to <sup>1</sup>H NMR measurement again. The tube was then heated at 80 °C, and its <sup>1</sup>H NMR were taken after 1 h and 13 h, respectively. <sup>1</sup>H NMR revealed that the reaction completed after 13 h at 80 °C. 1,4-Dioxane (25.7 μL, 0.3 mmol) was added to the NMR tube as an internal standard, and <sup>1</sup>H NMR showed that diphenylmethane-*d*<sub>5</sub> was obtained in 96% yield (0.288 mmol).

#### 4-8-9. The *tert*-butylation of *tert*-butyl phenylphosphonate (**1q**) in benzene-*d*<sub>6</sub> catalyzed by TfOH

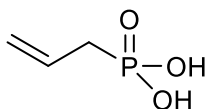
To an NMR tube was added *tert*-butyl phenylphosphonate **1q** (40.6 mg, 0.15 mmol) and C<sub>6</sub>D<sub>6</sub> (0.5 mL) and subjected to <sup>1</sup>H NMR measurement. Trifluoromethanesulfonic acid (1.3 μL, 10 mol%) was then added to the NMR tube. The tube was slightly shaken at room temperature and was subjected to <sup>1</sup>H NMR measurement after 0.5 h, 1.5 h, 3.5 h and 5 h, respectively. <sup>1</sup>H NMR showed that the reaction completed after 5 h and isobutene **4** was generated.

#### 4-8-10. <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR Spectral Data of the Products



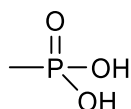
##### *Vinylphosphonic acid (2a)*.<sup>18a</sup>

Colorless oil (248.7 mg, 91%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ 5.70–5.66 (m, 2H), 5.64–5.63 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, D<sub>2</sub>O): δ 133.8, 126.7 (d, *J*<sub>C-P</sub> = 176.6 Hz). <sup>31</sup>P NMR (162 MHz, D<sub>2</sub>O): δ 16.7.



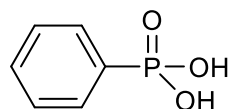
***Allylphosphonic acid (2e).***<sup>18b</sup>

White solid (274.8 mg, 89%). <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO): δ 8.89 (s, 2H), 5.90 (s, 1H), 5.34–5.27 (m, 2H), 2.74–2.71 (m, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO): δ 128.5 (d, *J*<sub>C-P</sub> = 20.0 Hz), 119.6 (d, *J*<sub>C-P</sub> = 10.9 Hz), 32.6 (d, *J*<sub>C-P</sub> = 140.1 Hz). <sup>31</sup>P NMR (162 MHz, (CD<sub>3</sub>)<sub>2</sub>CO): δ 28.4.



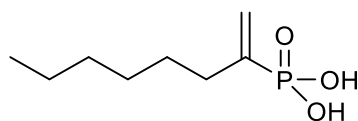
***Methylphosphonic acid (2f).***<sup>18c</sup>

Colorless oil (225.9 mg, 93%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ 1.28 (dt, *J* = 17.2 Hz, 5.2 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, D<sub>2</sub>O): δ 11.7 (d, *J*<sub>C-P</sub> = 135.7 Hz). <sup>31</sup>P NMR (162 MHz, D<sub>2</sub>O): δ 31.1.



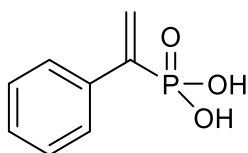
***Phenylphosphonic acid (2g).***<sup>6a</sup>

White solid (71.1 mg, 90%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ 7.63–7.57 (m, 2H), 7.45–7.41 (m, 1H), 7.37–7.32 (m, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, D<sub>2</sub>O): δ 132.3 (d, *J*<sub>C-P</sub> = 2.7 Hz), 130.5 (d, *J*<sub>C-P</sub> = 182.2 Hz), 130.4 (d, *J*<sub>C-P</sub> = 10.4 Hz), 128.7 (d, *J*<sub>C-P</sub> = 14.8 Hz). <sup>31</sup>P NMR (162 MHz, D<sub>2</sub>O): δ 17.2.



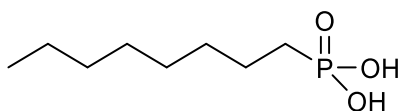
***Oct-1-en-2-ylphosphonic acid (2h).***<sup>18d</sup>

White solid (262.6 mg, 54%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.59 (s, 2H), 5.96 (d, *J* = 23.6 Hz, 1H), 5.63 (d, *J* = 49.6 Hz, 1H), 2.28–2.21 (m, 2H), 1.50–1.48 (m, 2H), 1.27–1.25 (m, 6H), 0.88–0.85 (m, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 139.9 (d, *J*<sub>C-P</sub> = 176.6 Hz), 127.4 (d, *J*<sub>C-P</sub> = 9.4 Hz), 31.8, 31.7, 28.9, 27.9 (d, *J*<sub>C-P</sub> = 5.7 Hz), 22.7, 14.1. <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>): δ 21.9.



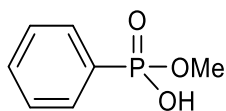
**1-Phenylvinylphosphonic acid (2i).**<sup>18e</sup>

White solid (377.3 mg, 81%). <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO): δ 9.94 (s, 2H), 7.65–7.64 (m, 2H), 7.47–7.43 (m, 3H), 6.32 (d, *J* = 22.0 Hz, 1H), 6.17 (d, *J* = 46.0 Hz, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO): δ 141.5 (d, *J*<sub>C-P</sub> = 174.5 Hz), 137.1 (d, *J*<sub>C-P</sub> = 10.4 Hz), 130.2, 128.7, 128.5, 127.7. <sup>31</sup>P NMR (162 MHz, (CD<sub>3</sub>)<sub>2</sub>CO): δ 17.6.



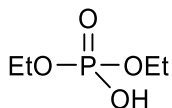
**n-Octylphosphonic acid (2l).**<sup>18f</sup>

White solid (92.2 mg, 95%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.04 (s, 2H), 1.78–1.69 (m, 2H), 1.65–1.55 (m, 2H), 1.36–1.26 (m, 10H), 0.89–0.86 (m, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 31.9, 30.5 (d, *J*<sub>C-P</sub> = 17.1 Hz), 29.1, 26.2, 24.7, 22.7, 22.1 (d, *J*<sub>C-P</sub> = 4.6 Hz), 14.1. <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>): δ 37.8.



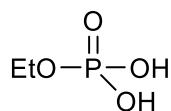
**Methyl phenylphosphonic acid (2n).**<sup>6a</sup>

White solid (70.6 mg, 82%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ 7.59–7.53 (m, 2H), 7.43–7.41 (m, 1H), 7.37–7.32 (m, 2H), 3.42 (dd, *J* = 4.0 Hz, 11.6 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, D<sub>2</sub>O): δ 132.6 (d, *J*<sub>C-P</sub> = 2.4 Hz), 131.0 (d, *J*<sub>C-P</sub> = 10.0 Hz), 128.8 (d, *J*<sub>C-P</sub> = 14.8 Hz), 128.4 (d, *J*<sub>C-P</sub> = 182.7 Hz), 52.5 (d, *J*<sub>C-P</sub> = 5.0 Hz). <sup>31</sup>P NMR (162 MHz, D<sub>2</sub>O): δ 20.4.



**Diethyl phosphoric acid (2o).**<sup>6a</sup>

White solid (71.7 mg, 93%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O):  $\delta$  3.88–3.84 (m, 4H), 1.12 (t,  $J$  = 7.0 Hz, 6H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, D<sub>2</sub>O):  $\delta$  63.5 (d,  $J_{C-P}$  = 5.4 Hz), 15.5 (d,  $J_{C-P}$  = 6.6 Hz). <sup>31</sup>P NMR (162 MHz, D<sub>2</sub>O):  $\delta$  0.6.



**Ethyl phosphoric acid (2p).**<sup>6a</sup>

Colorless oil (59.2 mg, 94%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O):  $\delta$  3.78–3.70 (m, 2H), 0.98 (dt,  $J$  = 2.4 Hz, 7.2 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, D<sub>2</sub>O):  $\delta$  63.5 (d,  $J_{C-P}$  = 5.1 Hz), 15.3 (d,  $J_{C-P}$  = 6.4 Hz). <sup>31</sup>P NMR (162 MHz, D<sub>2</sub>O):  $\delta$  0.2.

## 4-9. References

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## Chapter 6

### Conclusions

In summary, I have succeeded in developing new methods for the transformation of the readily available trialkyl phosphites (catalyzed by Brønsted acids) and triaryl phosphites (catalyzed by Pd) to valuable phosphonates such as H-phosphonates, alkylphosphonates, arylphosphonates via selective PO–R cleavages. And I have also disclosed that the obtained phosphonates can be further converted to the corresponding phosphonic acids catalyzed by Brønsted acids via PO–R cleavage under wet or dry processes. The mechanisms for these reactions were also studied.

In chapter 2, I found that water can determine the selectivity of the Brønsted acid-catalyzed C–O cleavage reactions of trialkyl phosphites: with water, the reaction occurs quickly 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. 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. The solid acid Nafion is also a very active catalyst for the reactions, as it can be readily used in large scale reactions, recovered and reused for at least five cycles without losing any catalytic activity. All these revealed the method's potential utility in industrial manufacturing. Mechanistic studies showed that the reaction perhaps takes place via a monomolecular mechanism.

In chapter 3, I have disclosed a simple palladium-PhX (X = OTf, I) catalyst system can efficiently catalyse the transformation of  $(\text{ArO})_3\text{P}$  to  $\text{ArP}(\text{O})(\text{OAr})_2$  from a combination of  $(\text{ArO})_3\text{P}/\text{PhX}$  (X = OTf, I). This an unprecedented palladium catalysed rearrangement can settle the historically long-unresolved last problem for the Michaelis–Arbuzov reaction and therefore complete it finally. This method is general in substrate scope as it can be readily extended to aryl phosphonites and phosphinites for synthesizing the corresponding aryl phosphinates and phosphine oxides. According to the mechanistic studies, I also proposed a possible mechanism.

In chapter 4, I have developed a wet and two dry methods to prepare phosphonic acids from phosphonate esters catalyzed by Brønsted acids. A variety of phosphonates could be efficiently protonated in water or, in the absence

of water, in toluene and benzene. Furthermore, selective monodealkylation of dialkyl phosphonates could be achieved by employing this Brønsted acid-catalyzed method in toluene under mild conditions. The reusable solid acid Nafion could be used as the catalyst for these reactions, that made the preparation of phosphonic acids simple and easy.

In this doctoral dissertation, I established new methods for the preparation of H-phosphonates (Chapter 2), alkylphosphonates (Chapter 2), arylphosphonates (Chapter 3) and phosphonic acids (Chapter 4) via selective catalytic PO–R bond cleavage of the corresponding trialkyl phosphites, triaryl phosphites and the obtained phosphonates.

## List of Publications

1. **C. Li**, Q. Wang, J. Q. Zhang, J. Ye, J. Xie, Q. Xu, L.-B. Han. 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. *Green Chem.* **2019**, *21*, 2916-2922.
2. **C. Li**, Y. Saga, S. Onozawa, S. Kobayashi, K. Sato, N. Fukaya, L.-B. Han. Wet and Dry Processes for the Selective Transformation of Phosphonates to Phosphonic Acids Catalyzed by Brønsted Acids. *J. Org. Chem.* **2020**, doi.org/10.1021/acs.joc.0c00550.
3. **C. Li**, L.-B. Han. *Tetrahedron Lett.* **to be submitted.**
4. **C. Li**, D. Han, L.-B. Han. *Org. Lett.* **to be submitted.**

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