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Magnesium Halide-promoted Ring-opening Reaction of Cyclic Ether in the Presence of Phosphine Halide

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A new route to the direct preparation of H-phosphinate esters has been explored. The ring-opening reaction of cyclic ether (tetrahydrofuran or tetrahydropyrane) was carried out with magnesium halide in the presence of phosphine halide ($PRCl_2$ or PCl_3). The process is straightforward and all the reagents are relatively cheap and readily available. Magnesium halide-mediated THF ring-opening (S_N2@C) and the subsequent S_N2@P elementary reactions that giving rise to the intermediate of haloalkyl phosphinates have been discussed based on our experimental findings (**Path I**: S_N2@C → S_N2@P). Another possible route, the direct S_N2 between THF (nucleophile) and phosphine halide (electrophile) that followed by THF ring opening by halide dissociated from phosphine halide (**Path II:** S_N2@P → S_N2@C), was also proposed. However, **path II** is the least likely reaction path because neutral THF is not a good nucleophile. H-phosphinate esters could be readily available in the subsequent hydrolysis process. Considering the ionic bond strength in magnesium halides and the nucleophilicity of halides dissociated from MgX_2 in protic solvents like water, $MgBr_2$ is recommended for ring-opening reactions of cyclic ethers.

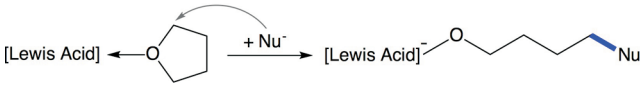
Keywords: Ring-opening reaction; Tetrahydrofurane; H-phosphinate ester; Magnesium; Bimolecular nucleophilic substitution.

INTRODUCTION

The direct incorporation of phosphorus-containing groups into the target molecules for the preparation of new compounds containing C-P bonds is a quite useful strategy for chemical transformation. It shows far-reaching influence in broad areas of chemistry.[1-6] For example, such compounds are valuable in transition-metal catalysts and organocatalysts.[7-17]

Tetrahydrofuran (THF) is a widely used solvent in many chemical reactions due to its good solubility towards various organic and inorganic substrates. It is generally believed that the ring-opening process takes place after the coordination of THF onto Lewis acid and followed by nucleophilic attack on α-carbon next to oxygen atom (Scheme 1).[18,19] The functionalization of THF to industrially useful feedstock has been achieved mostly by opening the cyclic ether ring. The first ring-opening of THF was reported a century ago. Up to now, various kinds of metal species, such as U,[20,21] Sm,[22,23] Ti,[24] Te,[25] Re,[26,27] Zr,[28-32] Al,[33,34] Fe,[35] Zn,[36] and Li,[37-42] as well as non-metals, such as B,[43-46] and H_2SO_4,[47] were employed in this type of catalytic ring-opening reactions. Note that the C-P bond in [Lewis Acid]-O$(CH_2)_4$-PR_3^+ or [Lewis Acid]-O$(CH_2)_4$-PR_2 is formed in the Lewis-acid assisted THF ring-opening reaction with phosphine derivatives as nucleophiles (Scheme 1).[48,49] Nevertheless, only few reports regarding P-O bond formation in the direct synthesis of H-phosphinate esters from THF with phosphine chlorides, which is catalyzed by HgX_2[50] or mediated by stoichiometric organozinc compound,[51] have been documented.

Scheme 1 Lewis acid-catalyzed THF ring-opening reaction by a nucleophile.



Organophosphorous compounds are essential in the synthesis of bioactive natural products.[52] Particularly, H-phosphinate ester ($(R^1O)HP(=O)R^2$) are important organophosphorus building blocks in the synthesis of medicinally relevant protease inhibitors and ATP-dependent ligases.[53-65] We thought THF could be an ideal substrate for the synthesis of H-phosphinate ester via the formation of new P-O bond if the THF ring-opening residual (-O$(CH_2)_4Nu^-$) or THF itself can act as a nucleophile to attack on the phosphine halides ($PR_nY_{(3-n)}$, Y: Cl or Br; n = 0 or 1) via the bimolecular substitution reaction (S_N2@P: bi-

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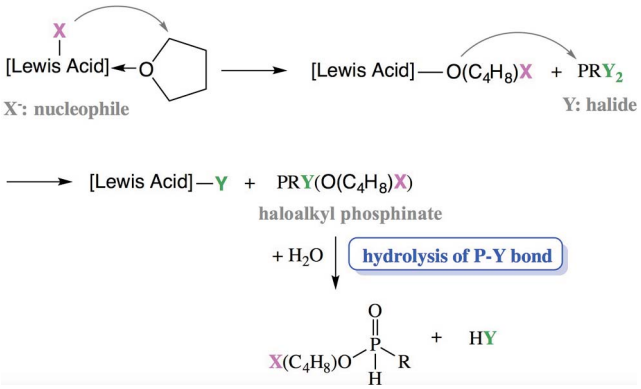
molecular nucleophilic substitution reaction at phosphorus center) (Scheme 2).[66-68] In this case, it is conceivable that a better nucleophile (Nu^-) than $PR_nY_{(3-n)}$ for THF ring opening is a prerequisite for realizing the subsequent P-O bond formation. This reaction proceeds with the nucleophilic attack of $-O(CH_2)_4Nu^-$ on $PR_nY_{(3-n)}$ (n = 0 or 1) after the THF ring opening by Nu^-.

Scheme 2 The employment of Lewis acid (a promoter and source of halogen nucleophile) and phosphine halide (electrophile) to the syntheses of haloalkyl phosphinate and the hydrolyzed product H-phosphinate ester.



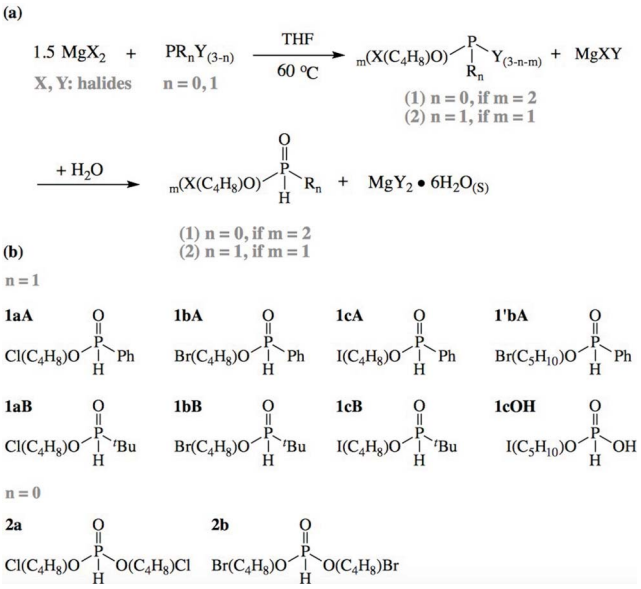
As known, THF is an inert molecule in Grignard reaction as solvent even under elevated temperature.[69-73] Ring-opening of THF catalyzed by Mg(II) could take place only in certain circumstances. Herein, we present some interesting results in anhydrous magnesium halides (MgX_2) promoted ring-opening reactions of cyclic ethers in the presence of phosphine chlorides as well as the discussion on plausible mechanisms of the reaction pathways.

RESULTS AND DISCUSSION

The formation of haloalkyl phosphinates intermediate and H-phosphinate esters

Ring-opening of THF was carried out in the reaction system of $PR_nY_{(3-n)}$ (R = Ph, ^{t}Bu, or Cl; Y = Cl, Br, or I; n = 0 or 1) and 1.5 folds of anhydrous MgX_2 (X = Cl, Br, or I) in THF solution at 60 °C (Scheme 3 and Table 1) for their respectively designated reaction time (Table 1). The general procedure for the ring-opening reaction of THF is described in the experimental section. After completion of the reaction (monitored by ^{31}P NMR), water was added to hydrolyze the intermediate of haloalkyl phosphinate ($(XR^1O)PYR$ ($-OR^1X$ = $-O(CH_2)_4X$)). The reaction eventually led to the formation of H-phosphinate ester ($(XR^1O)HP(=O)R$ after hydrolysis of the P-Y bond. In contrast, THF ring-opening reaction was not observed at ambient temperature. Additionally, the THF ring-opening process is not favored when the reaction was performed in the absence of halide source of magnesium halide. The products were carefully characterized by their ^{1}H,^{13}C, ^{31}P NMR and mass spectra.

Scheme 3 (a) The synthesis of haloalkyl phosphinate and H-phosphinate ester. (b) Structures for the H-phosphinate esters synthesized in this study.



Accordingly, the $MgCl_2$-mediated reaction of THF with $PPhCl_2$ or P^tBuCl_2 led to the formation of product **1aA** or **1aB** with quantitative conversion (entry 1 & 2 in Table 1). The isolated yields for **1aA** or **1aB** are 80% and 85%, respectively. Besides, colorless crystals of $MgCl_2{\cdot}6H_2O$ were obtained in $MgCl_2$-mediated reactions through the keeping of the final work-up solution for 72 hours at room temperature. The formation of $MgCl_2{\cdot}6H_2O$ was further confirmed by single crystal X-ray crystallographic study.[74] The use of $MgBr_2$ in the ring opening reaction gave similar results with phosphine sources $PPhBr_2$ and P^tBuBr_2, respectively (entries 3 & 4).

Interestingly, when the ring opening of THF was carried out in the presence of MgI_2 with $PPhCl_2$ and P^tBuCl_2, the iodo-substituented products of 1**cA** and 1**cB** were obtained (Scheme 3b, entries 5 & 6 in Table 1). The isolated yield of **1cA** is 70%, indicating some loss in yield during

Table 1. Ring-opening of cyclic ethers to the H-phosphinates esters and H-phosphonate ester[a]

Entry	Cyclic ether	MgX_2	PX_3	Product[b]	Conversion (isolated[c]) (%)
1[d]		$MgCl_2$	$PPhCl_2$	**1aA**	99 (80)
2[d]		$MgCl_2$	P^tBuCl_2	**1aB**	99 (85)
3[e]		$MgBr_2$	$PPhBr_2$	**1bA**	99
4[e]		$MgBr_2$	P^tBuBr_2	**1aB**	99
5[e]		MgI_2	$PPhCl_2$	**1cA**	99 (70)
6[e]		MgI_2	P^tBuCl_2	**1cB**	90
7[f]		$MgBr_2$	$PPhCl_2$	**1'bA**	80
8[d]		$MgCl_2$	PCl_3	**2a**	99 (99)
9[e]		$MgBr_2$	PCl_3	**2b**	99
10[e]		MgI_2	PCl_3	-	[g]

[a] Reaction conditions: Reactions were conducted in 1.5 mL THF or THP solution at 60 °C for 48 hours. Magnesium halide: 1.5 mmol; phosphine chloride: 1.0 mmol. [b] Products were characterized by ^{31}P-NMR, ^{1}H, ^{13}C-NMR and ESI mass. [c] The conversion is almost quantitative, however, the yields are reduced after work up and purification. [d] Reacted for 48-72 hours. **2a**: 48 hours; **1aA**: 50 hours; **1aB**: 72 hours. [e] Reacted for 1 hour. [f] Reacted for 2 hours. [g] **1cOH** was quantitatively obtained from decomposition of the expected product $HP(=O)(OC_5H_{10}I)_2$.

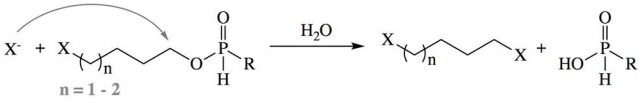
column chromatography. Actually, the byproduct of I-(C_4H_8)-I was detected. By observing the bis(iodoalkoxyl)-substituents on **1cA** and **1cB**, it is conceivable that halides exchange occurred between MgX_2 and $PR_nY_{(3-n)}$. This highlights the importance of MgX_2 because the X^- anion provide a good source of halogen nucleophile for THF ring opening of $MgX_2(THF)_m$ (m = 2 - 4) at elevated temperature (Scheme 3a). The reaction route will be discussed in the Mechanism section.

For PCl_3 (entries 8, 9 & 10), the reactivity of MgI_2 and $MgBr_2$ (both reacted for 1 hour) is different from that of $MgCl_2$ (48 hours). Two chloroalkoxyl or bromoalkoxyl chains were observed in the products for $MgCl_2$- or $MgBr_2$-promoted reactions (enrty 8 and 9). Contrarily, there was no expected product, $HP(=O)(OC_5H_{10}I)_2$, being detected by ^{31}P NMR spectrum but the quantitatively conversion of **1cOH** with one iodoalkoxyl chain obtained from the reaction of MgI_2 and PCl_3 (entry 10). Moreover, the formation of 1,4-diiodobutane was also observed in this reaction. Similar result was reported for the ring-opening of THF in the presence of H_3PO_4 and KI,[75] and the formation of **1cOH** and a large amount of 1,4-diiodobutane will be discussed later. Noteworthy, halide exchange between MgX_2 and PCl_3 was evidenced from the products of **2b** and **1cOH** (Scheme 3b, entry 9 & 10 in Table 1).

If this phenomenon can be proved, the duel roles as Lewis acid and source of halogen nucleophile for THF ring opening played by MgX_2 is established and confirmed. To validate this assumption of halides exchange between MgX_2 and $PR_nY_{(3-n)}$, the reaction of PBr_3 with 5 mol% of $MgCl_2$ in THF was carried out for 24 hours. The main product of bromoalkoxyl-substituted H-phosphinate ester **2b** was obtained (conversion yield: 90%), demonstrating the bromide anion dissociated from PBr_3 *via* $S_N2@P$ reaction unambiguously coordinated back to the catalyst containing Mg(II) and, in turn, catalyzing the formation of bis(bromoalkoxyl)-substituted product **2b**. Together with the products given by the reactions of stochiometric MgX_2 and PCl_3 in THF solution (entry 9 and 10 in Table 1), it clearly indicated that there was a halide exchange process between X^- and Cl^-.

The six-membered cyclic ether of tetrahydropyrane (THP) was subjected to the ring-opening reaction using 1.5-fold of $MgBr_2$ and $PPhCl_2$ at 60 °C for 2 hours (entry 7 in Table 1). Followed by hydrolysis, the formation of **1'bA** was achieved in the conversion yield of 80% (Scheme 3b). Compared to THF ring-opening reactions between MgX_2 and $PPhCl_2$ with quantitative conversion yield (entry 1 & 5 in Table 1), the lower yield of THP ring-opening reaction is partly due to the formation of 1,5-dibromopetane (Scheme 4). On the other hand, the reaction rate for THP ring opening was sluggish by using $MgCl_2$ with $PPhCl_2$ as reagents (not shown in Table 1). The reason for the severely attenuated reaction rate could be related to the ionic bond strength of magnesium halides ($MgCl_2 > MgBr_2 > MgI_2$) Therefore, compared to the $MgCl_2$-mediated THP ring-opening reaction, the much slower reaction rate of $MgCl_2$-mediated analogue can be attributed to the strongest Mg-Cl ionic bond among the three magnesium halides. Similar reactivity in HgX_2-catalyzed THF ring-opening reactions has been reported (reactivity: $HgCl_2 < HgBr_2 < HgI_2$).[50] In summary, the $MgBr_2$ could be the best choice among all the three halides used in THP ring-opening reactions.

Scheme 4 The formation of dihaloalkane *via* the nucleophilic attack of halide anion on haloalkoxyl substituent.



The formation of dihaloalkanes was found in $MgBr_2$- and MgI_2-mediated reactions (entry 5, 6, 7 and 10 in Table 1). In the case of MgI_2 with $PPhCl_2$ (entry 5), the desired product of $HP(=O)(O(C_4H_8)I)Ph$ (**1cA**) were assumed to be formed quantitatively; yet, decomposition of it to a large amount of $I\text{-}(C_4H_8)\text{-}I$ was observed during the work-up hydrolysis process and/or column chromatography. The formation of dihaloalkane can be correlated to the nucleophilicity of halides dissociated from MgX_2 in water solution. In aprotic solvents like THP or THF, the nucleophilicity of halides is in the order of $Cl^- > Br^- > I^-$. Nevertheless, the reverse trend is found in polar protic solvents like water.[76] In the case of stoichiometric $MgBr_2$-promoted THP reaction, the formation of bromoalkyl phosphinate intermediate of $P(O(C_5H_{10})Br)PhCl$ can be expected (entry 7); however, upon hydrolysis the nucleophilic attack of bromide on the α-carbon next to the oxygen atom in $–O(C_5H_{10})Br^-$ chain led to the formation of $Br\text{-}(C_5H_{10})\text{-}Br$ and **1'bA** (80% in conversion). The same result was observed in entry 6. Further along this line, in MgI_2-mediated THF ring-opening reaction using PCl_3 as reagent (entry 10), the fact that the formation of **1cOH** without the quantitative conversion yield of $HP(=O)(OC_5H_{10}I)_2$ is associated with the formation of 1,4-diiodobutane (Scheme 4).

The efficiency of THF ring-opening reactions can be further discussed, and summaries can be drawn from these results (Table 1). (1) The weaker the Mg-X bond, the easier the THF ring opening by X^- originated from MgX_2 (entry 1 vs. 5; entry 2 vs. 6). Interestingly, the rate of THF ring opening seems not depending on the nucleophilicity of halogen nucleophiles (X^-) in aprotic THF solvent ($Cl^- > Br^- > I^-$), but the availability of them in the reaction conditions. Again, the reactivity of MgX_2 in entry 8 – 10 clearly shows that $MgCl_2$ (48 hours) < $MgBr_2$ (1 hour) ≤ MgI_2 (1 hour), while the ionic bond strength is in the order of $MgCl_2 > MgBr_2 > MgI_2$. (2) The larger the steric hindrance of electrophile $PR_nY_{(3-n)}$, the slower the reaction rate of the second $S_N2@P$ reaction (c.f. the reaction time for obtaining products in entry 1, 2 and 8: PCl_3 (48 hour) > $PPhCl_2$ (50 hour) > P^tBuCl_2 (72 hour).

In the ring-opening reactions between THF or THP with $PR_nY_{(3-n)}$ (n = 0 or 1), we observed (3-n-m) (m = 1 or 2) haloalkoxyl chains in the the products of H-phosphinate ester derivatives $HP(=O)(ORX)_mR_n$ (if n = 0, m = 2; if n = 1, m = 1) (Scheme 3a). The number of $(\text{-}ORX)_m$ is always less than the number of $\text{-}Y^-$ substituent in $PR_nY_{(3-n)}$ by 1. This might be accounted for by the steric effect of –R and/or hindered -(ORX) substituent(s) on phosphorus-containing species. The same findings has been reported by Newman et al.[51]

Mechanisms

In anhydrous THF solution, two to four solvent molecules could coordinate to the $MgBr_2$.[77] These species are the tetrahedral $MgBr_2(THF)_2$ (I),[78] trigonal bipyramidal $MgBr_2(THF)_3$ (II),[78] and octahedral $MgBr_2(THF)_4$ (III).[77] For the later two compounds, two bromides occupy the axial positions as shown by their respective crystal structures. II and I can be obtained from the least stable III by dissociating one and then the second THF molecules from Mg(II).[77,78] Therefore, I is conceivable to be the plausible THF-coordinated active species of Lewis acid MgX_2 for THF ring opening reaction. Note that the formation of I (or II) is also an consequence of the oxophilic nature of Mg(II).[79]

The proposed mechanisms of Mg(II)-mediated formation of H-phosphinate ester derivatives have been presented in Figure 1. In the mechanisms, MgX_2 stands for magnesium halides and acts as a Lewis acid for THF coordination. Moreover, $PPhCl_2$ is the source of phosphine halide. In mechanism Ia of Figure 1, the ring opening of a coordinated THF solvent molecule in $MgX_2(THF)_2$ could be proceeded with the intramolecular nucleophilic attack of the anionic halide ligand X^- on the α-carbon of THF ($S_N2@C$).[80] This elementary step is facilitated with the increased electrophilicity of the α-carbon on one of the coordinated THF molecules. Furthermore, the substrate of PCl_2Ph thus interacts with the resultant tri-coordinated intermediate of MgX(THF)(ORX) ($\text{-}ORX : \text{-}OC_2H_8X^-$) via its halide substituent. By passing through a four-membered transition state composed of Mg(II), O, P, and Cl atoms ($S_N2@P$), the $MgXCl(THF)_2$ and the P(ORX)ClPh are obtained. Note that the MgX(THF)(ORX) is similar to the alkoxide ligand normally witnessed in catalysts of ring-opening polymerization. Interestingly, no THF polymerization reaction was observed partly due to the stoichiometric equivalence of electrophile of phosphine halides. After the hydrolysis of P(ORX)PhCl, the H-phosphinate esters of HP(=O)(ORX)Ph can be formed. In the proposed reaction mechanism, the halide exchange between MgX_2 and $PPhCl_2$ has been justified.

The other plausible magnesium halide-mediated mechanism starts with the formation of phosphine chloride-coordinated intermediate, $MgX_2(PPhCl_2)(THF)$ (mechanism Ib in Figure 1). Followed by the intramolecular

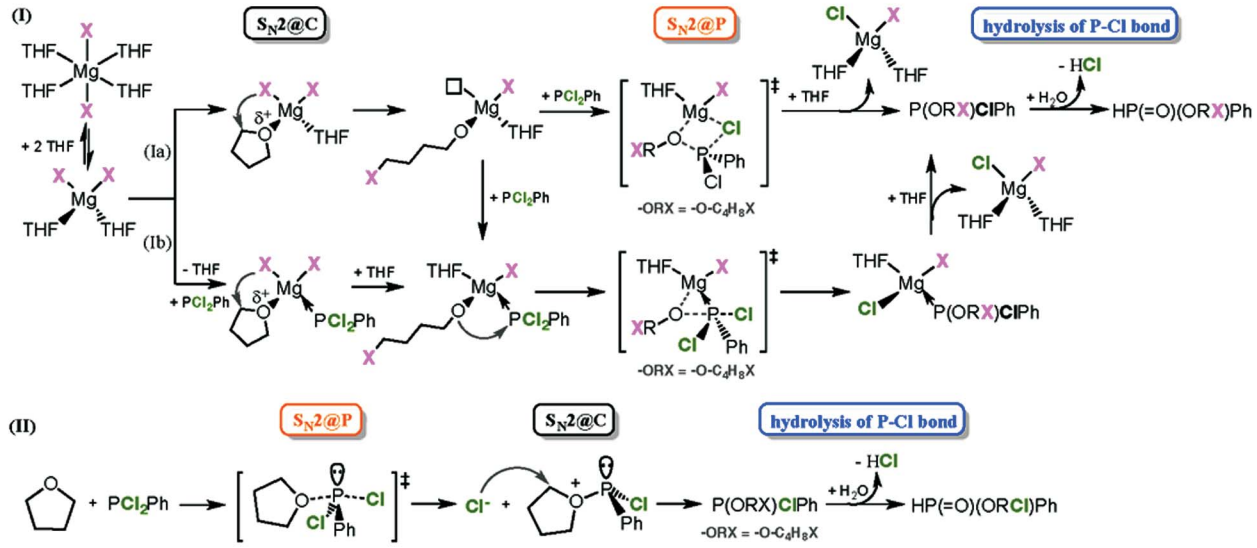


Fig. 1. Proposed mechanisms for the formation of haloalkyl phosphinate *via* the (I) Mg(II)-mediated and (II) direct THF ring-opening reactions (THF as nucleophile). H-phosphinate ester can be readily obtained from the hydrolysis of haloalkyl phosphinate. PCl_2Ph is used as an example. X: halides from $MgX_2(THF)_2$.

S_N2@C reaction between X^- and a coordinated THF molecule, the $MgX(PPhCl_2)(THF)(ORX)$ is resulted. This species could also be obtained from the coordination of $PPhCl_2$ to MgX(THF)(ORX), which is an intermediate in the mechanism Ia. Next, another S_N2@P reaction between haloalkoxide $–ORX^-$ and the coordinated $PPhCl_2$ can occur through an Mg-O-P three-membered transition structure. In the mean time, the leaving of Cl^- could coordinate back to Mg(II) center so as to yield the the MgXCl(THF)(P(ORX)PhCl). The P(ORX)PhCl is readily dissociated from the magnesium compound and ready for hydrolyzed to the final product of H-phosphinate ester, HP(=O)(ORX)Ph.

In addition to magnesium halide-assisted THF ring opening, the direct S_N2 reaction at phosphorus center (S_N2@P) between C_4H_8O (nucleophile) and $PPhCl_2$ (electrophile) that followed by THF ring opening by the dissociated nucleophile Y^- (S_N2@C) should be considered for completeness (mechanism II in Figure 1). The formation of P(ORX)PhCl intermediate *via* the direct S_N2@P mechanism is believed to be a high-energy barrier pathway because neutral THF is a weak neutral nucleophile.[50] No halide exchange will occur because there is no MgX_2 is involved in the reaction mechanism. Judging from the products shown in Scheme 3b, it is stated that this mechanism is not thermodynamically favorable route.[50]

In $MgX_2(THF)_2$-mediated reactions, the high yields of work-up products of HP(=O)(ORX)Ph unambiguously indicate that the THF ring was opened by X^- from $MgX_2(THF)_2$ rather than by $PPhCl_2$. The later would give rise to a new P-C bond instead of P-O bond observed herein. This is in sharp contrast to the ring-opening reactions of THF with Lewis acid of $B(C_5F_5)_3$ and Lewis base of sterically congested secondary phosphines.[81]

In summary, H-phosphinate esters, HP(=O)(R)(OR'X) (R = Ph, ^{t}Bu; R' = C_4H_8, C_5H_{10}; X = Cl, Br, I), were prepared from the reaction of THF/THP with MgX_2 in the presence of $PR_nY_{(3-n)}$ (n = 0 or 1; Y = Cl or Br). Two major reaction mechanisms including MgX_2-mediated and direct S_N2 reaction between THF/THP and phosphine chlorides towards the formation of these haloalkyl phosphinates and eventually of the hydrolyzed H-phosphinate esters have been proposed and analyzed. Lewis acid MgX_2 plays a dual role for THF coordination and the source of halogen nucleophile. It is therefore, in such MgX_2-mediated ring-opening reactions between cyclic ethers and phosphine halides, halide exchange between MgX_2 and $PR_nY_{(3-n)}$ was observed. Finally, considering the reactivity of MgX_2 and the nucleophilicity of halides in protic solvents like water, anhydrous $MgBr_2$ is recommended for ring-opening reactions between magnesium halides, cyclic ethers and phosphine chlorides as well as for minimizing the formation of dihaloalkane side products during hydrolysis.

EXPERIMENTAL

General information: All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques or in a nitrogen-flushed Glovebox. Freshly distilled solvents were used. All processes of separations of the products were performed by centrifugal thin layer chromatography. GC-MS analysis was performed on an Agilent 5890 gas chromatograph (Restek Rtx-5MS fused silica capillary column: 30 m, 0.25 mm, 0.5 μm) with an Agilent® 5972 mass selective detector. Electrospray ionization-high resolution mass spectra (ESI-HRMS) and atmospheric pressure chemical ionization mass spectra (APCI-MS) were recorded on a LTQ Orbitrap XL (Thermo Fisher Scientific) mass spectrometer. Routine ^{1}H NMR spectra were recorded on a Varian-400 spectrometer at 400.00 MHz. The chemical shifts are reported in ppm relative to internal standard TMS (δ = 0.0). ^{31}P and ^{13}C NMR spectra were recorded at 162.1 and 100.7 MHz, respectively. The chemical shifts for the former and the latter are reported in ppm relative to internal standards H_3PO_4 (δ = 0.0) and $CHCl_3$ (δ = 77), respectively.

Formation of HP(=O)(OC_4H_8Cl)Ph (1aA), HP(=O)(OC_4H_8Cl)(^{t}Bu) (1aB) and HP(=O)(OC_4H_8Cl)$_2$ (2a): Into a 100 mL round-bottomed flask was placed 1.5 mmol $MgCl_2$ (0.143 g) with 1.5 ml THF. The solution was then stirred at 60 °C till all the $MgCl_2$ was dissolved. Subsequently, 1.0 mmol of the phosphine source 0.189 g $PPhCl_2$ (0.159 g P^{t}BuCl_2 or 0.137 g PCl_3) was added and the solution changed to colorless. It was then stirred at 60 °C for 48 to 72 hrs depended on the nature of reactant. Subsequently, purified water was added to the crude mixture which caused the hydrolysis of the product and dissolving the salt. Next, the mixture was extracted with diethyl ether for three times. The combined organic layer was then dried with anhydrous $MgSO_4$. Lastly, the concentrated organic layer was purified by column chromatography to yield the desired product **1aA** (**laB** or **2a**) with ethyl acetate (ethyl acetate/methanol = 20/1 or ethyl acetate). Note here that these types of H-phosphinate esters tend to be partly decomposed during the process of column chromatography under prolonged eluting hour. Therefore, the isolated yields greatly vary with the purification procedures.

Spectroscopic data for HP(=O)(OC_4H_8Cl)Ph (1aA) ^{1}H NMR ($CDCl_3$, δ/ppm): 7.60 (d, $^{1}J_{P\text{-}H}$ = 565 Hz, 1H, P-H), 7.82-7.76 (q, 2H, *o*-Ph), 7.63-7.61 (t, 1H, *p*-Ph), 7.56-7.51 (m, 2H, *m*-Ph), 4.15-4.10 (m, 2H, P-OCH_2-), 3.59-3.56 (t, 2H, -CH_2Cl), 1.93-1.88 (m, 4H, -CH_2CH_2-); ^{13}C NMR ($CDCl_3$, δ/ppm): 129.52 (d, $^{1}J_{P\text{-}C}$ = 133 Hz, 1C, P-C(*ipso*)), 133.20, 133.17 (d, 2C, *o*-Ph), 130.90, 130.79 (d, 2C, *p*-Ph), 128.86, 128.73 (d, 2C, *m*-Ph), 64.88 (d, $^{2}J_{P\text{-}C}$ = 6.5 Hz, 1C, P-OCH_2-), 44.32 (s, 1C, -CH_2Cl), 28.64 (s, 1C, -CH_2-CH_2Cl), 27.76, 27.70 (d, 1C, -CH_2-CH_2OP); ^{31}P NMR ($CDCl_3$, δ/ppm): 25.42 (d, P-H, $^{1}J_{P\text{-}H}$ = 565 Hz); MS (EI): *m/z* 197 [M-Cl]$^+$. ESI-MS: *m/z* 233 [M+H]$^+$. **Spectroscopic data for HP(=O)(OC_4H_8Cl)(^{t}Bu) (1aB)** ^{1}H NMR ($CDCl_3$, δ/ppm): 6.73 (d, $^{1}J_{P\text{-}H}$ = 515 Hz, 1H, P-H), 4.19-4.17 (m, 1H, P-OCH_2-), 4.07-4.03 (m, 1H, P-OCH_2-), 3.61-3.58 (m, 2H, -CH_2Cl), 1.92-1.86 (m, 4H, -CH_2CH_2-), 1.14 (d, $^{2}J_{P\text{-}H}$ = 17.6 Hz, 9H, -$C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, δ/ppm): 30.98 (d, $^{1}J_{P\text{-}C}$ = 95.7 Hz, 1C, P-C), 65.35 (d, $^{2}J_{P\text{-}C}$ = 7.7 Hz, 1C, P-OCH_2-), 44.25 (s, 1C, -CH_2Cl), 28.63 (s, 1C, -CH_2-CH_2Cl), 27.68, 27.63 (d, 1C, -CH_2-CH_2OP), 22.54 (s, 3C, -$C(CH_3)_3$); ^{31}P NMR ($CDCl_3$, δ/ppm): 49.86 (dm, P-H, $^{1}J_{P\text{-}H}$ = 515 Hz); MS (EI): *m/z* 177 [M-Cl]$^+$. ESI-MS: *m/z* 213 [M+H]$^+$. **Spectroscopic data for HP(=O)(OC_4H_8Cl)$_2$ (2a)** ^{1}H NMR ($CDCl_3$, δ/ppm): 6.84 (d, $^{1}J_{P\text{-}H}$ = 697 Hz, 1H, P-H), 4.16-4.11 (q, 2H, P-OCH_2-), 3.61-3.58 (m, 2H, -CH_2Cl), 1.93-1.86 (m, 4H, -CH_2CH_2-); ^{13}C NMR ($CDCl_3$, δ/ppm): 64.86 (d, $^{2}J_{P\text{-}C}$ = 7.7 Hz, 1C, P-OCH_2-), 44.26 (s, 1C, -CH_2Cl), 28.56 (s, 1C, -CH_2-CH_2Cl), 27.70, 27.64 (d, 1C, -CH_2-CH_2OP); ^{31}P NMR ($CDCl_3$, δ/ppm): 7.92 (dm, P-H, $^{1}J_{P\text{-}H}$ = 697 Hz). Elemental analysis calculated for $C_8H_{18}IO_2P$: C, 36.52; H, 6.51. Found: C, 36.18; H, 6.42.

Formation of HP(=O)(OC_4H_8Br)(Ph) (1bA), HP(=O)H(OC_4H_8Br)(^{t}Bu) (1bB) and HP(=O)(OC_4H_8Br)$_2$ (2b): A100 mL round-bottomed flask was charged with 1.5 mmol Mg powder (0.036 g), 1.5 mmol 1,2-dibromoethane (0.282 g) and 1.5 ml THF. The solution was stirred at 60 °C for 5 hrs till the solution color changed to gray. Presumably, quantitative $MgBr_2$ was formed accompanied with released ethylene. Subsequently, 1.0 mmol of the phosphine source 0.189 g $PPhCl_2$ (0.159 g P^{t}BuCl_2 or 0.137 g PCl_3) was added and the color of the solution changed to yellow (colorless or orange, respectively). The solution was stirred at 60 °C for 1 hr, the same workup procedures proceeded as in 4.1. Almost pure 2b was obtained from the organic layer. Product 1bA (or 1bB) was purified through the column chromatography with the ethyl acetate (or ethyl acetate/methanol = 10/1).

Spectroscopic data for HP(=O)(OC_4H_8Br)(Ph) (1bA) ^{1}H NMR ($CDCl_3$, δ/ppm): 7.60 (d, $^{1}J_{P\text{-}H}$ = 565 Hz, 1H, P-H), 7.82-7.77 (m, 2H, *o*-Ph), 7.64-7.60 (m, 1H, *p*-Ph), 7.55-7.51 (m, 2H, *m*-Ph), 4.18-4.06 (m, 2H, -OCH_2-P), 3.45-3.42 (t, 2H, -CH_2Br), 2.04-1.97 (m, 2H, -CH_2-CH_2OP), 1.92-1.86 (m, 2H, -CH_2-CH_2Br); ^{13}C NMR ($CDCl_3$, δ/ppm): 129.50 (d, $^{1}J_{P\text{-}C}$ = 132 Hz, 1C, P-C(*ipso*)), 132.99, 132.97 (d, 2C, *o*-Ph), 130.69, 130.57 (d, 2C, *p*-Ph), 128.68, 128.54 (d, 2C, *m*-Ph), 64.55 (d, $^{2}J_{P\text{-}C}$ = 6.4 Hz, 1C, P-OCH_2-), 32.71 (s, 1C, -CH_2Br), 28.60 (s, 1C, -CH_2-CH_2Br), 28.82, 28.75, (d, 1C, -CH_2-CH_2OP); ^{31}P NMR ($CDCl_3$, δ/ppm): 25.94 (d, $^{1}J_{P\text{-}H}$ = 564 Hz, P-H); Elemental analysis calculated for $C_{10}H_{14}BrO_2P$: C, 43.35; H, 5.09; Found: C, 43.07; H, 5.17. MS (FAB): *m/z* 197.0 [M-Br]$^+$. **Spectroscopic**

data for HP(=O)H(OC_4H_8Br)(^{t}Bu) (1bB) ^{1}H NMR ($CDCl_3$, δ/ppm): 6.71 (d, $^1J_{P\text{-}H}$ = 515 Hz, 1H, P-H), 4.19-4.15 (m, 1H, -OCH_2-P), 4.04-4.00 (m, 1H, -OCH_2-P), 3.46-3.43 (m, 2H, -CH_2Br), 2.01-1.93 (m, 2H, -CH_2-CH_2OP), 1.89-1.82 (m, 2H, -CH_2-CH_2Br), 1.12 (d, $^2J_{P\text{-}H}$ = 18.0 Hz, 9H, -$C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, δ/ppm): 31.02 (d, $^1J_{P\text{-}C}$ = 93.4 Hz, 1C, P-C), 65.24 (d, $^2J_{P\text{-}C}$ = 8.3 Hz, 1C, P-OCH_2-), 32.80 (s, 1C, -CH_2Br), 28.82 (s, 1C, -CH_2-CH_2Br), 28.95, 28.90 (d, 1C, -CH_2-CH_2OP), 22.57 (s, 3C, -$C(CH_3)_3$); ^{31}P NMR ($CDCl_3$, δ/ppm): 49.87 (dm, $^1J_{P\text{-}H}$ = 515 Hz, P-H); MS (EI): *m/z* 177 $[M\text{-}Br]^+$. ESI-MS: *m/z* 259 $[M+H]^+$. **Spectroscopic data for HP(=O)($OC_4H_8Br)_2$ (2b)** ^{1}H NMR ($CDCl_3$, δ/ppm): 6.84 (d, $^1J_{P\text{-}H}$ = 698 Hz, 1H, P-H), 4.16-4.11 (q, 2H, P-OCH_2-), 3.47-3.44 (q, 2H, -CH_2Br), 2.04-1.96 (m, 2H, -CH_2-CH_2OP), 1.91-1.84 (m, 2H, -CH_2-CH_2Br); ^{13}C NMR ($CDCl_3$, δ/ppm): 64.60 (d, $^2J_{P\text{-}C}$ = 6.1 Hz, 1C, P-OCH_2-), 32.75 (s, 1C, -CH_2Br), 28.49 (s, 1C, -CH_2-CH_2Br), 28.71, 28.65 (d, 1C, -CH_2-CH_2OP); ^{31}P NMR ($CDCl_3$, δ/ppm): 7.94 (dm, P-H, $^1J_{P\text{-}H}$ = 699 Hz); Elemental analysis calculated for $C_8H_{18}IO_2P$: C, 27.30; H, 4.87. Found: C, 26.86; H, 4.78.

Formation of HP(=O)(OC_4H_8I)(Ph) (1cA), HP(=O)(OC_4H_8I)(^{t}Bu) (1cB) and HP(=O)(OC_4H_8I)(OH) (1cOH): Into a 100 mL round-bottomed flask was added 1.5 mmol Mg (0.036 g), 3.0 mmol iodomethane (0.426 g) and 1.5 ml THF. The solution was stirred at 40 °C for 2.5 hr and its color changed to white. Then, the temperature was raised to 60 °C before adding 1.0 mmol phosphine reactant 0.189 g $PPhCl_2$ (0.159 g P^{t}BuCl_2 or 0.137 g PCl_3). The color of solution changed to yellow for 1cA (or white and orange for 1cB and 1cOH, respectively). After 1 hr in reaction, the same workup procedures proceeded as in 4.1. Pure compound 1cOH could be obtained from the organic layer. While products 1cA and 1cB were purified through the column chromatography with the EA and EA/Hexane = 5/1, respectively.

Spectroscopic data for HP(=O)(OC_4H_8I)(Ph) (1cA) ^{1}H NMR ($CDCl_3$, δ/ppm): 7.59 (d, $^1J_{P\text{-}H}$ = 567 Hz, 1H, P-H), 7.78-7.72 (m, 2H, *o*-Ph), 7.60-7.56 (m, 1H, *p*-Ph), 7.52-7.47 (m, 2H, *m*-Ph), 4.13-4.02 (m, 2H, -OCH_2-P), 3.18-3.15 (t, 2H, -CH_2I), 1.93-1.78 (m, 4H, -CH_2CH_2-); ^{13}C NMR ($CDCl_3$, δ/ppm): 129.46 (d, $^1J_{P\text{-}C}$ = 144 Hz, 1C, P-C(*ipso*)), 133.09 (s, 2C, *o*-Ph), 130.79, 130.67 (d, 2C, *p*-Ph), 128.75, 128.62 (d, 2C, *m*-Ph), 64.42 (d, $^2J_{P\text{-}C}$ = 7.4 Hz, 1C, P-OCH_2-), 5.58 (s, 1C, -CH_2I), 29.33 (s, 1C, -CH_2-CH_2I), 31.13, 31.06, (d, 1C, -CH_2-CH_2OP); ^{31}P NMR ($CDCl_3$, δ/ppm): 26.36 (d, P-H, $^1J_{P\text{-}H}$ = 570 Hz). ESI-MS: *m/z* 325 $[M+H]^+$. **Spectroscopic data for HP(=O)(OC_4H_8I)(^{t}Bu) (1cB)** ^{1}H NMR ($CDCl_3$, δ/ppm): 6.71 (d, $^1J_{P\text{-}H}$ = 515 Hz, 1H, P-H), 4.19-4.14 (m, 1H, -OCH_2-P), 4.05-4.00 (m, 1H, -OCH_2-P), 3.24-3.20 (m, 2H, -CH_2I), 1.97-1.78 (m, 4H, -CH_2CH_2-), 1.18 (d, $^2J_{P\text{-}H}$ = 18.0 Hz, 9H, -$C(CH_3)_3$). 49.87 (d, P-H, $^1J_{P\text{-}H}$ = 515 Hz). ESI-MS: *m/z* 305 $[M+H]^+$. **Spectroscopic data for HP(=O)(OC_4H_8I)(OH) (1cOH)** ^{1}H NMR ($CDCl_3$, δ/ppm): 6.78 (d, $^1J_{P\text{-}H}$ = 705 Hz, 1H, P-H), 10.90 (s, 1H, P-OH), 4.10, 4.05 (q, 2H, P-OCH_2-), 3.23-3.19 (m, 2H, -CH_2I), 1.96-1.79 (m, 4H, -CH_2CH_2-); ^{13}C NMR ($CDCl_3$, δ/ppm): 64.86 (d, $^2J_{P\text{-}C}$ = 7.7 Hz, 1C, P-OCH_2-), 44.26 (s, 1C, -CH_2Cl), 28.56 (s, 1C, -CH_2-CH_2Cl), 27.70, 27.64 (d, 1C, -CH_2-CH_2OP); ^{31}P NMR ($CDCl_3$, δ/ppm): 7.96 (dm, P-H, $^1J_{P\text{-}H}$ = 705 Hz). ESI-MS: *m/z* 287 $[M+Na]^+$.

Formation of HP(=O)($OC_5H_{10}Br$)(Ph) (1'bA): Into a 100 mL round-bottomed flask was charged 1.5 mmol Mg powder (0.036 g), 1.5 mmol 1,2-dibromoethane (0.282 g) and 1.0 ml diethyl ether. The solution was stirred at 35 °C for 2 hrs before solvent was removed in vacuum. It leaved a white powder of $MgBr_2$ in flask. Subsequently, the mixture solution containing phosphine reactant, 1.0 mmol tetrahydropyran (THP) and 1.0 mL 1,2-dichloroethane was added to the reaction flask. After 2 hrs in reaction, the same workup procedures proceeded as in 4.1. While product 1'bA was purified through the column chromatography with gradient mixed solvents (diethyl acetate/hexane = 1/1 to 5/1).

Spectroscopic data for HP(=O)($OC_5H_{10}Br$)(Ph) (1'bA) ^{1}H NMR ($CDCl_3$, δ/ppm): 7.60 (d, $^1J_{P\text{-}H}$ = 564 Hz, 1H, P-H), 7.82-7.77 (m, 2H, *o*-Ph), 7.63-7.61 (t, 1H, *p*-Ph), 7.56-7.51 (m, 2H, *m*-Ph), 4.12-4.08 (m, 2H, -OCH_2-P), 3.46-3.40 (m, 2H, -CH_2Br), 1.92-1.1.55 (m, 6H, -$CH_2CH_2CH_2$-); ^{31}P NMR ($CDCl_3$, δ/ppm): 25.32. ESI-MS: *m/z* 291 $[M+H]^+$.

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