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An Extremely Efficient Three-Component Reaction of Aldehydes/Ketones, Amines, and Phosphites (Kabachnik−Fields Reaction) for the Synthesis of α-Aminophosphonates Catalyzed by Magnesium Perchlorate

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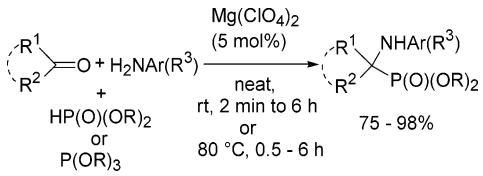

Commercially available magnesium perchlorate is reported as an extremely efficient catalyst for the synthesis of α-aminophosphonates. A three-component reaction (3-CR) of an amine, an aldehyde or a ketone, and a di-/trialkyl phosphite (Kabachnik−Fields reaction) took place in one pot under solvent-free conditions to afford the corresponding α-aminophosphonates in high yields and short times. The use of solvent retards the rate of the reaction and requires a much longer reaction time than that for neat conditions. The reactions involving an aldehyde, an aromatic amine without any electron-withdrawing substituent, and a phosphite are carried out at rt. The reactions involving cyclic ketones, aromatic amines with an electron-withdrawing substituent, and aryl alkyl ketone (e.g., acetophenone) require longer reaction times at rt or heating. Magnesium perchlorate was found to be superior to other metal perchlorates and metal triflates during the reaction of 4-methoxybenzaldehyde, 2,4-dinitroaniline, and dimethyl phosphite. The catalytic activity of various magnesium compounds was influenced by the counteranion, and magnesium perchlorate was found to be the most effective. The reaction was found to be general with di-/trialkyl phosphites and diaryl phosphite. The $Mg(ClO_4)_2$-catalyzed α-aminophosphonate synthesis in the present study perhaps represents a true three-component reaction as no intermediate formation of either an imine or α-hydroxy phosphonate was observed that indicated the simultaneous involvement of the carbonyl compound, the amine, and the phosphite in the transition state.

Introduction

The α-aminophosphonate moiety is a versatile and novel pharmacophore due to the broad spectrum of biological activity exhibited by compounds bearing this structural unit.[1] Thus, the development of new synthetic methodologies for α-aminophosphonates[2] has attracted the attention of medicinal/organic chemists. Recently, various methodologies have been developed for the synthesis of α-aminophosphonates.[3] However, still there remains a need to develop a more efficient method, particularly keeping in view the disadvantages associated with some of the reported procedures such as the requirement of solvent, additional reagents, heating, long time, costly and moisture sensitive catalysts, special apparatus, etc., and the reported methodologies do not work well with electron-deficient amines such as nitro anilines.

While designing a new catalyst, we thought that the use of a more effective electrophilic activation agent should accelerate the overall reaction rate, and a metal salt derived from a strong protic acid should be an ideal contender. The large negative H_0 value of −14.1 of TfOH[4] makes TfOH the strongest protic acid, and thus, metal triflates drew attention as catalysts.[3f,g,k,q] However, TfOH is liberated from metal triflates and may be the actual catalytic agent.[5] The in situ generation of TfOH might be the reason for the potential side reactions (e.g., dehydration, rearrangement, etc.) with acid-sensitive substrates or deactivation

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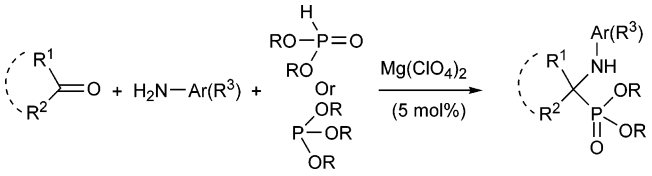
SCHEME 1. $Mg(ClO_4)_2$-Catalyzed 3-CR of an Aldehyde/Ketone, an Amine, and Di-/Trialkyl Phosphite Leading to the Formation of α-Aminophosphonate



of the amine substrates due to salt formation. Thus, metal triflate-catalyzed reactions are often carried out in the presence of stoichiometric amounts of additional reagents such as molecular sieves, $MgSO_4$, etc. This brings the attention to triflimides[6] as $HNTf_2$ is a weaker Brønsted acid than TfOH[7] and ligand exchange is not common with triflimides.[8] However, metal triflimides are costly, very few are available commercially, and they require additional efforts and costly reagents to prepare.[9] Hence, we focused our attention on catalysts derived from $HClO_4$ as it is weaker than TfOH. Recently, we reported metal perchlorates as efficient electrophilic activation catalysts for acylation, imine formation, thia-Michael addition, and acylal formation reactions.[10]

Results and Discussion

Herein, we report that $Mg(ClO_4)_2$ is an extremely efficient catalyst for the formation of α-aminophosphonate by a one-pot, three-component reaction of an aldehyde/ketone, an amine, and a di-/trialkyl phosphite under solvent-free conditions (Scheme 1).

To determine the best experimental conditions, the reaction of 4-methoxybenzaldehyde (**1**) as a representative less electrophilic aldehyde, 2,4-dinitroaniline (**2**) as an electron-deficient and sterically hindered amine, and dimethyl phosphite (DMP) was considered as the model (Table 1). The best results were obtained in the presence of $Mg(ClO_4)_2$ at rt affording the desired α-aminophosphonate dimethyl [(2,4-dinitrophenylamino)-(4-methoxyphenyl)methyl]phosphonate (**3**) in 85% yield after 6 h at rt and after 30 min at 80 °C (entries 1 and 2, Table 1). The order of mixing the substrates did not influence the product yield. The use of organic solvents required longer reaction times (entries 3−5, Table 1), but no significant amount of **3** was formed in carrying out the reaction in water (entry 8, Table 1). However, the use of magnesium perchlorate hydrate [$Mg(ClO_4)_2 \cdot 6H_2O$] was less effective (entries 6 and 7, Table 1). A similar decrease in the catalytic property of $Mg(ClO_4)_2 \cdot 6H_2O$ compared to that of $Mg(ClO_4)_2$ has been observed in the acylation reactions.[10a,11]

We planned to evaluate the catalytic property of $Mg(ClO_4)_2$ with other metal perchlorates during the three-component reaction of **1**, **2**, and DMP (Table 2). The best results were obtained with $Mg(ClO_4)_2$ either at rt for 6 h or at 80 °C for 30 min. In all

TABLE 1. $Mg(ClO_4)_2$-Catalyzed Synthesis of α-Aminophosphonate during the Reaction of 1, 2, and DMP under Various Conditions[a]

entry	catalyst	solvent	T (°C)	time (h)	yield[b,c] (%)
1	$Mg(ClO_4)_2$	neat	80	0.5	85
2	$Mg(ClO_4)_2$	neat	rt	6	85
3	$Mg(ClO_4)_2$	DCM	rt	24	81
4	$Mg(ClO_4)_2$	MeCN	rt	24	81
5	$Mg(ClO_4)_2$	THF	rt	24	80
6	$Mg(ClO_4)_2 \cdot 6H_2O$	neat	rt	10	40[d]
7	$Mg(ClO_4)_2 \cdot 6H_2O$	neat	80	6	60[d]
8	$Mg(ClO_4)_2$	H_2O	rt	24	nil[d]

[a] **1** (2.5 mmol) was treated with **2** (2.5 mmol) and DMP (2.5 mmol) in the presence of the catalyst (5 mol %) under solvent-free conditions (except for entries 3−5 and 8). [b] Yield of the isolated and purified **3**. [c] The product was characterized by the IR, ^1H and ^{13}C NMR, and MS. [d] The unreacted starting materials remained unchanged (TLC).

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TABLE 2. Various Metal Perchlorate Catalyzed Synthesis of 3 during the Reaction of 1, 2, and DMP under Various Conditions[a]

entry	catalyst	*T* (°C)	time (h)	yield[b,c] (%)
1	$Mg(ClO_4)_2$	80	0.5	85
2	$Mg(ClO_4)_2$	rt	6	85
3	$LiClO_4$	rt	10	trace[d]
4	$LiClO_4$	80	6	40[d]
5	LPDE	rt	24	20[d,e]
6	NH_4ClO_4	80	1	25[d]
7	NH_4ClO_4	rt	10	5[d]
8	$Zn(ClO_4)_2 \cdot 6H_2O$	80	1	60[d]
9	$Zn(ClO_4)_2 \cdot 6H_2O$	rt	10	30[d]
10	$Fe(ClO_4)_2 \cdot xH_2O$	80	1	40[d]
11	$Fe(ClO_4)_2 \cdot xH_2O$	rt	10	12[d]
12	$Fe(ClO_4)_3 \cdot xH_2O$	80	1	40[d]
13	$Fe(ClO_4)_3 \cdot xH_2O$	rt	10	15[d]
14	$Co(ClO_4)_2 \cdot 6H_2O$	80	1	40[d]
15	$Co(ClO_4)_2 \cdot 6H_2O$	rt	10	20[d]
16	$Cu(ClO_4)_2 \cdot 6H_2O$	80	1	60[d]
17	$Cu(ClO_4)_2 \cdot 6H_2O$	rt	10	5[d]
18	$ZrO(ClO_4)_2 \cdot 6H_2O$	80	1	50[d]
19	$ZrO(ClO_4)_2 \cdot 6H_2O$	rt	10	20[d]
20	$BiO(ClO_4)_2 \cdot xH_2O$	80	1	70[d]
21	$BiO(ClO_4)_2 \cdot 6H_2O$	rt	10	30[d]
22	$In(ClO_4)_3 \cdot xH_2O$	80	1	60[d]
23	$In(ClO_4)_3 \cdot 6H_2O$	rt	10	20[d]
24	$Yb(ClO_4)_3$	80	1	30[d,f]
25	$Yb(ClO_4)_3$	rt	10	nil[d,f]

[a] **1** (2.5 mmol) was treated with **2** (2.5 mmol) and DMP (2.5 mmol) in the presence of the catalyst (5 mol % except for entry 5) under solvent-free conditions (except for entries 5, 23, and 24). [b] Yield of the isolated and purified **3**. [c] The product was characterized by the IR, ^1H and ^{13}C NMR, and MS. [d] The unreacted starting materials remained unchanged (TLC). [e] 3 equiv of $LiClO_4$ (as a 5 M solution in Et_2O) was used. [f] A 40% (wt/vol) aqueous solution was used.

cases where the desired aminophosphonate **3** was formed in poor yield, the unreacted starting materials remained unchanged (TLC).

The present method is far more superior to the use of $LiClO_4$,[12] which required 2−10 equiv of $LiClO_4$, additional reagent (e.g., TMSCl), and solvent. The superiority of $Mg(ClO_4)_2$ over $LiClO_4$ was due to the better electrophilic activation ability of Mg^{+2} ion compared to that of Li^+ as the former cation has a higher charge to size ratio (the Z^2/r values of Mg^{+2} and Li^+ are 5.56 and 1.35 $e^2\ m^{-10}$, respectively).[13] The inferior catalytic property of $Fe(ClO_4)_2 \cdot 6H_2O$, $Zn(ClO_4)_2 \cdot 6H_2O$, $Co(ClO_4)_2 \cdot 6H_2O$, and $Cu(ClO_4)_2 \cdot 6H_2O$ was due to the lower Z^2/r values of 5.19, 5.33, 5.40, and 5.48 $e^2\ m^{-10}$, respectively, of the Fe^{+2}, Zn^{+2}, Co^{+2}, and Cu^{+2} ions.[12] However, although the Z^2/r values of 8.82, 11.39, 13.85, and 22.22 $e^2\ m^{-10}$, respectively, of the Bi^{+3}, In^{+3}, Fe^{+3}, and Zr^{+4} ions are higher than that of the Mg^{+2} ion the lower hydrolysis constants (pK^a_h) values[13] of 1.58, 3.70, 2.19, and 0.22 of these ions compared to a value of 11.42 of Mg^{+2} make these metal hydrates less effective as the associated water molecules decreased the electrophilicity of the central metal ions. Thus, the lack of appreciable catalytic activity of $Mg(ClO_4)_2 \cdot 6H_2O$ was due to the decrease of the electrophilic property of the Mg^{+2} ion by the water molecules in the hydrate.

The superiority of the present methodology over some of the recently reported procedures was established by comparison of the result obtained with the $Mg(ClO_4)_2$-catalyzed reaction with that of other reported catalysts/systems (Table 3).

TABLE 3. Comparison of the Catalytic Efficiency of $Mg(ClO_4)_2$ with Various Catalysts for the Synthesis of 3 during the Reaction of 1, 2, and DMP[a]

entry	catalyst	solvent	*T* (°C)	time (h)	yield[b,c] (%)
1	$Mg(ClO_4)_2$	neat	80	0.5	85
2	$Mg(ClO_4)_2$	neat	rt	6	85
3	LiOTf	neat	80	6	20[d]
4	$Mg(OTf)_2$	neat	80	6	50[d]
5	$Al(OTf)_3$	neat	80	6	20[d]
6	$Cu(OTf)_2$	neat	80	6	40[d]
7	$Sc(OTf)_3$	neat	80	6	50[e]
8	$Yb(OTf)_3-MgSO_4$	DCM	rt	48	trace[f]
9	$In(OTf)_3-MgSO_4$	THF	80	48	10[g]
10	$InCl_3$	THF	rt	24	trace[h]
11	$ZrCl_4$	MeCN	rt	24	trace[i]
12	$Cu(BF_4)_2$	neat	80	24	30
13	$[bmIm]BF_4$	$[bmIm]BF_4$	rt	24	25[j,k]

[a] **1** (2.5 mmol) was treated with **2** (2.5 mmol) and DMP (2.5 mmol) in the presence of the catalyst (5 mol % except for entry 13) under solvent-free conditions (except for entries 8−11 and 13). [b] Yield of the isolated and purified **3**. [c] The product was characterized by the IR, ^1H and ^{13}C NMR, and MS. [d] Compare with ref 3g. [e] Compare with ref 3k. [f] Compare with ref 3q. [g] Compare with ref 3f. [h] Compare with 3p. [i] Compare with ref 20. [j] Compare with ref 3j. [k] The catalyst (ionic liquid) itself was used as solvent.

TABLE 4. Comparison of the Catalytic Efficiency of Various Magnesium Salts for the Synthesis of 3 during the Reaction of 1, 2, and DMP[a]

entry	catalyst	solvent	*T* (°C)	time (h)	yield[b,c] (%)
1	$Mg(ClO_4)_2$	neat	80	0.5	85
2	$Mg(ClO_4)_2$	neat	rt	6	85
3	$MgSO_4$	neat	80	1	20[d]
4	$MgSO_4$	neat	rt	24	5[d]
5	$MgSO_4$	DCM	rt	24	nil[d]
6	$MgSO_4$	DCE	reflux	4	30[d]
7	$MgSO_4$	THF	reflux	4	nil[d]
8	$MgCl_2$	neat	80	1	5
9	$MgCl_2$	neat	rt	24	nil
10	$MgBr_2$	neat	80	1	10
11	$MgBr_2$	neat	rt	24	nil
12	MgI_2	neat	80	1	10
13	MgI_2	neat	rt	24	nil
14	$Mg(OTf)_2$	neat	80	6	50[e]

[a] **1** (2.5 mmol) was treated with **2** (2.5 mmol) and DMP (2.5 mmol) in the presence of the catalyst (5 mol %) under solvent-free conditions (except for entries 5−7). [b] Yield of the isolated and purified **3**. [c] The product was characterized by the IR, ^1H and ^{13}C NMR, and MS. [d] Compare with ref 3f,q. [e] Compare with ref 3g.

To find out the influence of the counteranion on the catalytic property, various magnesium salts were used as the promoter during the reaction of **1**, **2**, and DMP (Table 4). The far more superior catalytic activity of $Mg(ClO_4)_2$ over the other magnesium salts correlates well with the acidic strength of the corresponding protic acids (except for TfOH).[15]

To establish the generality, various aldehydes/ketones, amines, and DMP or diethyl phosphite (DEP) were subjected to a one-pot reaction (3-CR) catalyzed by $Mg(ClO_4)_2$ (Table 5).

Excellent results were obtained during the reaction of aryl/heteroaryl/alkyl/aryl alkyl aldehydes/ketones with aryl/heteroaryl/alryl alkyl amines and dimethyl/ethyl phosphite. The reaction was compatible with various functional groups such as Cl, OMe, NO_2, OH, NMe_2, CN, and CO_2Me that do not interfere by competitive complex formation with the catalyst. Excellent chemoselectivity was observed for substrates contain-

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TABLE 5. Synthesis of α-Aminophosphonate during the Reaction of Various Aldehydes/Ketones, Amines, and DMP/DEP in the Presence of Anhydrous $Mg(ClO_4)_2$[a]

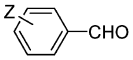
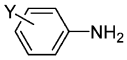
Entry	Aldehyde	Amine	Phosphite	Time (min)	Yield (%)[b]
					
1	Z = H	Y = H	DMP	2	98
2	Z = H	Y = H	DEP	2	98
3	Z = H	Y = 3,4,5-tri-OMe	DMP	10	93
4	Z = 4-OMe	Y = H	DMP	2	96
5	Z = 4-OMe	Y = H	DEP	5	95
6	Z = 4-OMe	Y = 4-OH	DMP	5	90
7	Z = 4-OMe	Y = 4-OMe	DMP	5	95
8	Z = 4-OMe	Y = 4-NO_2	DMP	10	98
9	Z = 4-OMe	Y = 3-NO_2	DMP	5	95
10	Z = 4-OMe	Y = 2-NO_2	DMP	15	95[c]
11	Z = 4-OMe	Y = 2,4-di-NO_2	DMP	30	85[c,d]
12	Z = 4-OMe	Y = 4-CN	DMP	10	80
13	Z = 4-OMe	Y = 4-CO_2Me	DMP	5	75
14	Z = 4-Cl	Y = H	DMP	5	95
15	Z = 4-Cl	Y = 4-NO_2	DMP	10	90[c]
16	Z = 4-Cl	Y = 3-NO_2	DMP	10	90[e]
17	Z = 4-NO_2	Y = 4-NO_2	DMP	10	97[e]
18	Z = 4-NO_2	Y = 4-NO_2	DEP	5	92[e]
19	Z = 4-OH	Y = H	DMP	5	95
20	Z = 4-NMe_2	Y = H	DMP	5	85
21	Z = 2,4-di-OMe	Y = NO_2	DMP	10	88[c,d]
22	Z = 2,4-di-OMe	Y = 2,4-di-NO_2	DMP	30	80[c,d]
23	Z = 2,4,6-tri-OMe	Y = H	DMP	15	91
24	Z = 2,4,6-tri-OMe	Y = 2,4-di-NO_2	DMP	60	80[c,d]

Table 5 (Continued)

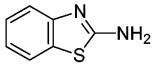
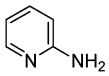
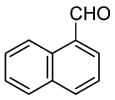
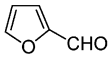
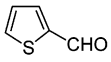
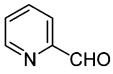
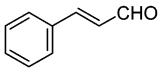
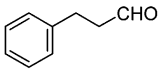
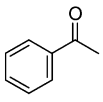
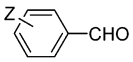
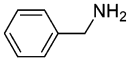
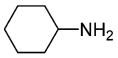
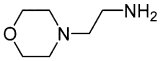
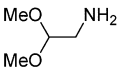
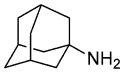
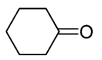
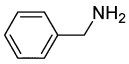
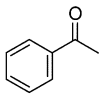
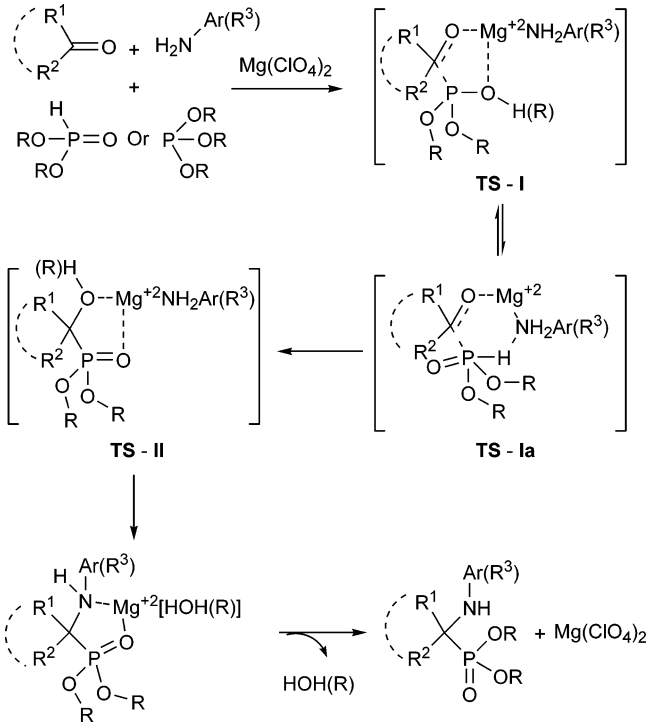
Entry	Aldehyde	Amine	Phosphite	Time (min)	Yield (%)[b]
25	Z = 3,4,5-tri-OMe	Y = H	DMP	10	96
26	Z = 3,4,5-tri-OMe	Y = 3,4,5-tri-OMe	DMP	10	95
27	Z = 4-OMe		DMP	30	80[c]
28	Z = 4-OMe		DMP	10	90
					
29		Y = H	DMP	5	90
30		Y = H	DEP	10	88
					
31		Y = H	DMP	5	92
32		Y = H	DEP	5	90
33		Y = H	DEP	50	90
34		Y = H	DMP	5	95
35		Y = H	DMP	5	90
36		Y = H	DMP	10	75
37		Y = H	DMP	15	85
					
38		Y = H	DMP	6 h	90[f]
39		Y = H	DEP	8 h	92[f]
					
40		Y = H	DMP	6 h	80[e,g]

Table 5 (Continued)

Entry	Aldehyde	Amine	Phosphite	Time (min)	Yield (%)[b]
41			DEP	8 h	75[c]
42	Z = H		DMP	2	95
43	Z = 4-OMe		DMP	2	90
44	Z = 4-OMe		DMP	10	95
45	Z = 4-OMe	 X = CH_2	DMP	5	95
46	Z = 4-OMe	X = O	DMP	10	90
47	Z = 4-OMe		DMP	2	98
48	Z = 4-OMe		DMP	15	80
49	Z = 4-OMe		DMP	5	95
50	Z = 4-OMe		DMP	15	90
51			DMP	6 h	92[f]
52			DEP	6 h	90[f]
53			DEP	6 h	80[e,h]
54			DEP	6 h	85[f]

[a] The aldehyde/ketone (2.5 mmol) was treated with the amine (2.5 mmol) and DMP/DEP (2.5 mmol) in the presence of $Mg(ClO_4)_2$ (5 mol %) at rt (except for entries 10, 11, 21, 22, 24, 27, and 53) under solvent-free conditions. [b] Yield of the purified α-aminophosphonate, characterized by IR, ^1H and ^{13}C NMR, and MS. [c] The reaction was carried out at 80 °C. [d] The reaction carried out at rt took 6 h to give 85% yield. [e] The reaction was carried out with 1.5 equiv of the phosphite. [f] A 90% yield was obtained when the reaction was carried out at 80 °C for 45 min. [g] The product was formed in 80 and 85% yields at rt after 20 h under neat conditions and under reflux in DCE after 4 h, respectively. [h] The product was formed in 90% yield in DCE under reflux after 2 h.

SCHEME 2. Role of $Mg(ClO_4)_2$ for α-Aminophosphonate Formation during the 3-CR Involving an Aldehyde, an Amine, and Di-/Trialkyl Phosphite



ing a halogen atom (entries 14−16, Table 5) and having a double bond conjugated to a carbonyl group (entry 35, Table 5) that did not experience any competitive aromatic nucleophilic substitution of the halogen atom and conjugate addition to the α,*β*-unsaturated carbonyl group, respectively. No competitive nucleophilic methyl ether cleavage was observed for substrates having an aryl *O*-Me group (entries 3−13, 21−28, and 43−50, Table 5), although phosphites possess good nucleophilic property.[16] The reaction with dimethyl acetal of aminoacetaldehyde (entry 49, Table 5) further exemplified the case of chemoselectivity and mildness of the reaction as no competitive nucleophilic substitution of the methoxy group or cleavage of the acetal moiety took place.

To evaluate the efficiency of this catalyst system as a general methodology with respect to the phosphite, 4-methoxybenzaldehyde and aniline were treated with various di-/trialkyl phosphites under the catalytic influence of $Mg(ClO_4)_2$ (Table 6).

The role of $Mg(ClO_4)_2$ is depicted in Scheme 2. It has been anticipated that the formation of α-aminophosphonate from the reaction of an aldehyde, an amine, and a phosphite involves a two-step process:[17] (i) the nucleophilic addition of the amine to the carbonyl group forming an imine followed by (ii) the nucleophilic addition of the phosphite to the imine.[18−20] However, no imine formation was observed (IR, NMR, MS) when 4-methoxybenzaldehyde was treated with 2,4-dinitroaniline in the presence

TABLE 6. Synthesis of α-Aminophosphonate during the Reaction of 1, Aniline, and Various Phosphites in the Presence of $Mg(ClO_4)_2$[a]

entry	phosphite	time (min)	yield[b,c] (%)
1	$HP(O)(OMe)_2$	2	96
2	$HP(O)(OEt)_2$	5	95
3	$P(OEt)_3$	10	90
4	$HP(O)(OBu^n)_2$	10	91
5	$P(OBu^n)_3$	20	83
6	$P(OPr^i)_3$	25	80
7	$HP(O)(OPh)_2$	5	98

[a] **1** (2.5 mmol) was treated with aniline (2.5 mmol) and the phosphite (2.5 mmol) in the presence of $Mg(ClO_4)_2$ (5 mol %) at rt under solvent-free conditions. [b] Yield of the isolated and purified α-aminophosphonate. [c] The product was characterized by IR, ^1H and ^{13}C NMR, and MS.

of $Mg(ClO_4)_2$ (5 mol %) at 80 °C for 6 h. The alternative pathway involving an intermediate formation of α-aminophosphonate by nucleophilic addition of the phosphite to the carbonyl carbon followed by nucleophilic displacement of the hydroxyl group by the amine[21] also appears unlikely as the treatment of 4-methoxybenzaldehyde with dimethyl phosphite in the presence of $Mg(ClO_4)_2$ (5 mol %) at 80 °C for 6 h did not produce any significant amount of the corresponding α-hydroxyphosphonate (IR, NMR, MS). Thus, in the absence of intermediate formation of the imine and the hydroxyphosphonate, this represents a truly 3-CR in which all three reactants/components are simultaneously involved in the product formation. We, therefore, propose that coordination of the Mg^{+2} ion with the carbonyl oxygen atom, the hydroxyl/alkoxyl group of the di-/trialkyl phosphite, and the nitrogen atom of the amine followed by the electrostatic attraction between the electrophilic carbonyl carbon atom with the lone pair of electrons of the phosphorus forms the **TS-I**, which undergoes rearrangement toform the **TS-II**. The intramolecular nucleophilic displacement of the hydroxyl/alkoxyl group, complexed with the $Mg(ClO_4)_2$ in the **TS-II**, by the nitrogen atom of the amine complexed with the $Mg(ClO_4)_2$ affords the α-aminophosphonate and liberates the $Mg(ClO_4)_2$.

We have described herein commercially available anhydrous $Mg(ClO_4)_2$ as a new and extremely efficient catalyst for synthesis of α-aminophosphonate by a three-component, one-pot reaction. With the increasing concern for need of green synthetic procedures, the advantages such as the (i) solvent-free reaction,[22] (ii) high yields, (iii) excellent chemoselectivity, and (iv) ease of product isolation/purification fulfill the triple bottom line philosophy of green chemistry[23] and make the present methodology environmentally benign.

Experimental Section

Typical Procedures for α-Aminophosphonate Synthesis. Reactions with Dialkyl/Aryl Phosphites. Dimethyl [(2,4-Dinitrophenylamino)(4-methoxyphenyl)methyl]phosphonate (Table

(14) (a) Yatsimirksii, K. B.; Vasil'ev V. P. *Instability Constants of Complex Compounds*; Pergamon, Elmsford, NY, 1960. (b) Bjerrum, Schwarzenbach, G., Sillen, L. G., Eds. *Stability Constants of Metal-Ion Complexes: PartII. Inorganic Ligands*; The Chemical Society, London, 1958.

(15) The pK_a values of aqueous $HClO_4$, H_2SO_4, HI, HBr, and HCl are −10, −9, −9, −8, and −6.1, respectively. Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Mill Valley, CA, 1960.

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(19) Szabó, A.; Jászay, Z. M.; Hergeds, L.; Tke, L.; Petneházy, I. *Tetrahedron Lett.* **2003**, *44*, 4603.

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(22) Garrett, R. L. In *Designing Safer Chemicals*; Garrett, R. L., De Vito, S. C., Eds.; American Chemical Society Symposium Series 640; American Chemical Society: Washington, DC, 1996; Chapter 1.

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5, Entry 11). The mixture of 4-methoxybenzaldehyde (**1**) (0.68 g, 5 mmol) and $Mg(ClO_4)_2$ (56 mg, 5 mol %) was stirred magnetically for 10−15 min, after which time 2,4-dinitroaniline (**2**) (0.91 g, 5 mmol) and DMP (0.55 g, 5 mmol) were added and the reaction mixture was stirred at rt for 6 h. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford a yellow solid (1.8 g) which on passing through a column of silica gel and elution with EtOAc−hexane (80:20) afforded dimethyl [(2,4-dinitrophenylamino)(4-methoxyphenyl)methyl]phosphonate (**3**) (1.75 g, 85%): mp 101 °C; IR (KBr) ν 1516, 1618, 2955, 3315 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.62 (d, 3 H, J = 10.68 Hz), 3.73 (d, 3 H, J = 10.68 Hz), 3.80 (s, 3 H), 4.90−4.99 (dd, 1 H, $^1J_{P-H}$ = 7.02 Hz, J = 22.51 Hz). 6.78 (d, 1 H, J = 9.4 Hz), 6.92 (d, 2 H, J = 8.6 Hz), 7.36−7.30 (dd, 2 H, J = 2.2, 8.7 Hz), 8.14−8.18 (dd, 1 H, J = 2.5, 9.4 Hz), 9.13 (d, 1 H, J = 2.3 Hz), 9.36 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 54.3 (d, *C*HP ,$^1J_{P-C}$ = 154.62 Hz), 54.7, 55.9, 115.3, 124.5, 125.1, 129.2, 130.7, 132.2, 137.6, 147.7, 147.9, 160.6; ^{31}P ($CDCl_3$; 121 MHz) δ 27.4 (m); MS (APCI) m/z = 411 $(M)^+$, 302 $[(M - P(O)(OMe)_2; 100]^+$. Anal. Calcd for $C_{16}H_{18}N_3O_8P$: C, 46.72; H, 4.41; N, 10.22. Found: C, 46.69; H, 4.39; N, 10.20. Using this procedure, repeating the reaction of **1** (2.72 g, 20 mmol), **2** (3.64 g, 20 mmol), and DMP (2.2 g, 20 mmol) in the presence of $Mg(ClO_4)_2$ (0.22 g, 5 mol %) afforded **3** (7.2 g, 87%) after the usual workup and purification. The remaining reactions were carried out following this general procedure. On each occasion, the spectral data (IR, NMR, and MS) of prepared known compounds were found to be identical with those reported in the literature. The following are a few representative examples using heteroaryl amine, aryl alkyl ketone, and sterically hindered aliphatic amine, respectively.

Dimethyl [(Benzothiazol-2-ylamino)(4-methoxyphenyl)methyl]phosphonate (Table 5, Entry 27). The treatment of **1** (0.34 g, 2.5 mmol) with 2-aminobenzothiazole (0.37 g, 2.5 mmol) and DMP (0.27 g, 2.5 mmol) in the presence of $Mg(ClO_4)_2$ (28 mg, 5 mol %) under magnetic stirring at 80 °C for 30 min followed by usual workup and chromatographic purification [silica gel: EtOAc−hexane (60:40) as eluent] afforded the dimethyl [(benzothiazol-2-ylamino)(4-methoxyphenyl)methyl]phosphonate (0.75 g, 80%) as a brownish yellow solid: mp 170 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.54 (d, 3 H, J = 10.6 Hz), 3.75 (s, 3 H), 3.80 (d, 3 H, J = 10.7 Hz), 5.54−90 (d, 1 H,$^1J_{P-H}$ = 21.63 Hz), 6.86−7.54 (m, 8 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 54.2, 54.5, 55.7, 56.2, 114.9, 119.8, 121.2, 122.3, 126.3, 127.3, 129.9, 131.6, 152.4, 160.2, 166.4; MS (APCI) m/z 378 $(M)^+$, 269 $[(M - P(O)(OMe)_2]^+$. Anal. Calcd for $C_{17}H_{19}N_2O_4PS$: C, 53.96; H, 5.06; N, 7.40; S, 8.47. Found: C, 53.94; H,5.04.; N, 7.38; S, 8.45.

Dimethyl (1-Phenyl-1-phenylaminoethyl)phosphonate (Table 5, Entry 40). The treatment of acetophenone (0.30 g, 2.5 mmol) with aniline (0.23 g, 2.5 mmol) and DMP (0.27 g, 2.5 mmol) in the presence of $Mg(ClO_4)_2$ (28 mg, 5 mol %) under magnetic stirring at 80 °C for 6 h followed by usual workup and chromatographic purification [silica gel: EtOAc−hexane (50:50) as eluent] afforded the dimethyl (1-phenyl-1-phenylaminoethyl)phosphonate (0.61 g, 80%) as brownish yellow solid: mp 128 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.97 (d, 3 H, J = 16.5 Hz), 3.53−3.66 (m, 6 H), 6.38−7.81 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 54.7, 117.3, 119.0, 128.0, 128.6, 129.2; MS (APCI) m/z 305 $(M)^+$, 196 $[(M - P(O)(OMe)_2]^+$. Anal. Calcd for $C_{16}H_{20}NO_3P$: C, 62.9; H, 6.6; N, 4.5. Found: C, 62.89; H, 6.5; N, 4.49.

Dimethyl [(Adamantan-1-ylamino)-(4-methoxyphenyl)methyl]phosphonate (Table 5, Entry 50). The treatment of **1** (0.34 g, 2.5 mmol) with 1-adamantylamine (0.37 g, 2.5 mmol) and DMP (0.27 g, 2.5 mmol) in the presence of $Mg(ClO_4)_2$ (28 mg, 5 mol %) under magnetic stirring at rt for 15 min followed by usual workup and chromatographic purification [silica gel: EtOAc−hexane (95:5) as eluent] afforded the dimethyl [(adamantan-1-ylamino)(4-methoxyphenyl)methyl]phosphonate (0.85 g, 90%) as white solid: mp 101 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43−1.60 (m, 12 H), 1.87 (s, 1 H), 1.97 (s, 2 H), 3.46 (d, 3 H, J = 10.30 Hz), 3.77−3.81 (2s, 9 H), 4.21−4.29 ($^1J_{P-H}$ = 24.4 Hz), 6.84 (d, 2 H, J = 8.2 Hz), 7.33 (d, 2 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.1, 37, 44.2, 52.1, 52.8, 53, 53.6, 54.3, 55.0, 55.7, 114.2, 129.6, 129.7, 132.3, 159.4; MS (APCI) m/z 379 $(M)^+$, 270 $[(M - P(O)(OMe)_2]^+$. Anal. Calcd for $C_{20}H_{30}NO_4P$: C, 63.31; H, 7.97; N, 3.69. Found: C, 63.18; H, 7.95; N, 3.68.

Reactions with Trialkyl Phosphites. Di-*n*-butyl [(4-Methoxyphenyl)phenylaminomethyl]phosphonate (Table 6, Entry 5). The treatment of **1** (0.34 g, 2.5 mmol) with aniline (0.23 g, 2.5 mmol) and tri-*n*-butyl phosphite (0.62 g, 5 mmol) in the presence of $Mg(ClO_4)_2$ (28 mg, 5 mol %) under magnetic stirring at rt for 20 min followed by usual workup and chromatographic purification [silica gel: EtOAc−hexane (25:75) as eluent] afforded the di-*n*-butyl [(4-methoxyphenyl)phenylaminomethyl]phosphonate (0.84 g, 83%) as a greenish black solid: mp 60 °C; IR (KBr) ν 1605, 2959, 3308 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81−0.91 (m, 6 H), 1.2−1.6 (m, 8 H), 3.59−4.05 (m, 7 H), 4.74 (d, 1 H, $^1J_{P-H}$ = 22.1), 6.56−7.38 (m, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 18.5, 18.6, 32.3, 32.5, 54.2, 55.2, 56.3, 66.8, 113.8, 118.2, 127.7, 128.8, 146.4, 159.3; ^{31}P ($CDCl_3$; 121 MHz) δ 29.19 (d, J = 11.78 Hz); MS (MALDI TOF TOF) m/z 405 $(M)^+$, 212 $[(M - P(O)(O^nBu)_2]^+$. Anal. Calcd for $C_{22}H_{32}NO_4P$: C, 65.17; H, 7.95; N, 3.45. Found: C, 65.14; H, 7.93; N, 3.43.

Diisopropyl [(4-Methoxyphenyl)phenylaminomethyl]phosphonate (Table 6, Entry 6). Treatment of **1** (0.34 g, 2.5 mmol) with aniline (0.23 g, 2.5 mmol) and triisopropyl phosphite (0.52 g, 2.5 mmol) in the presence of $Mg(ClO_4)_2$ (28 mg, 5 mol %) under magnetic stirring at rt for 25 min followed by usual workup and chromatographic purification [silica gel: EtOAc−hexane (35:65) as eluent] afforded the diisopropyl [(4-methoxyphenyl)phenylaminomethyl]phosphonate (0.75 g, 80%) as a faded white solid: mp 103 °C; IR (KBr) ν 1602, 2929, 2979, 3307 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, 3 H, J = 6.17 Hz), 1.21−1.32 (m, 9 H), 3.76 (s, 3 H), 4.41−4.73 (m, 3 H), 6.56−7.39 (m, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 23.7, 54.8, 55.2, 56.8, 71.8, 113.8, 118.1, 128.1, 129.1, 146.5, 146.7, 159.1; ^{31}P ($CDCl_3$; 121 MHz) δ 27.30 (d, J = 13.58 Hz); MS (APCI) m/z 377 $(M)^+$, 212 $[(M^+ - P(O)(O^iPr)_2]^+$. Anal. Calcd for $C_{20}H_{28}NO_4P$: C, 63.65; H, 7.48; N, 3.71. Found: C, 63.62; H, 7.46; N, 3.69.

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Supporting Information Available: General experimental details, scanned spectra, and spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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