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Highly efficient synthesis of α-aminophosphonates catalyzed by hafnium(IV) chloride

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ABSTRACT

A highly efficient one-pot method for the synthesis of a variety of α-aminophosphonates via the one-pot three-component reaction of aldehyde, amine, and phosphite has been developed by using only 2 mol% $HfCl_4$ as the catalyst. The NMR evidence strongly indicated the catalytic roles of Hf(IV) on the activation of aldehyde, phosphite, and imine intermediate.

As structural mimics of natural amino acids, aminophosphonic acids and their esters have been extensively investigated as transition-state analog inhibitors of a huge variety of enzymes with physiological and pathologcial importance, such as metallo-proteases,[1] aspartic proteases,[2] phosphatases,[3] ligases,[4] and glycotranferases.[5] As a result, natural and synthetic aminophosphonic acids have exhibited a broad range of biological activities to bacterial/viral/fungal infection, neurotransmission, cardiovascular misfunction, and plant/insect growth.[6] Recent research have further extended their applications as anticancer[7] and antituberculosis[8] agents.

Among the available synthetic methods for α-aminophosphates, the three-component reaction of aldehyde, amine, and phosphite, also known as Kabachnik-Fields reaction,[9] has gained much attention due to its one-pot manner and convenience in parrallel synthesis of diverse structural analogs. It has been well recognized that solvent-free conditions are preferred due to the elimiation of water in the reaction. However, clogging of α-aminophosphonate product in the absence of solvent prohibited the completion of the reaction in many cases. In the past decade, various Brønsted and Lewis acids catalysts, such as CF_3CO_2H,[10] $InCl_3$,[11] $TaCl_5$,[12] lanthanide triflates,[13] and $Mg(ClO_4)_2$,[14] and microwave conditions have been employed to improve the synthetic efficiency of the Kabachnik-Fileds reaction in different organic solvents. However, the applications of these catalysts are still not satisfactory due to their own limitations such as high cost, toxcity, specificity to aryladehyde/arylamine, and sensitivity to moisture. In addition, the detailed catalytic mechanisms of these catalysts have not been thoroughly eludicated.

Among the reported catalysts, $ZrOCl_2 \cdot 8H_2O$[15] attracted our attention in our synthesis of alkyldiamine-based bis-α-aminophosphates because of its catalytic activity and non-toxicity. Meanwhile, we also noticed that $HfCl_4$, a closely related Group IV metal salt, exhibited even superior activities in various metal-catalyzed reactions.[16] Inspired by these reports, we tested the possiblity to utilized $HfCl_4$ to promote the Kabachnik-Fileds reaction. In this paper, we report the employment of $HfCl_4$ as a highly efficient and robust catalyst for the synthesis of a diversity of α-aminophosphonates via the one-pot three-component reaction of aldehyde, amine, and phosphite. Compared to the reactions promoted by Zr(IV) salts, $HfCl_4$-catalyzed formation of α-aminophosphates is not only faster and cleaner but also requires less amount of catalyst (2 mol%) in ethanol. ^{31}P and ^{1}H NMR data strongly indicated the effects of Hf(IV) on the activation of both reactants and imine intermediate.

In the preliminary experiments, benzaldehyde, aniline, and dimethylphosphite (1:1:1.05 equiv) were reacted in the presence or absence of 10 mol% of various metal catalysts in ethanol ([aldehyde]=[amine]=1.0 M) at room temperature without inert gas protection. The results listed in Table 1 clearly showed that $Mg(ClO_4)_2$ exhibited almost no catalytic activity when compared to the control reaction without catalyst (incomplete at 48 h). In contast, all Zr(IV)-catalyzed reactions went to completion in 12–14 h with ~90% isolated yields of α-aminophosphate **1**. Interestingly, $HfCl_4$ significantly shortened the reaction time to only 6 h and racemic **1** was isolated in 98% yield. It was also observed that the reaction time of $HfCl_4$-catalyzed reaction was significantly prolonged at lower reaction concentrations. In contrast, the $HfCl_4$-catalyzed reaction under solvent-free

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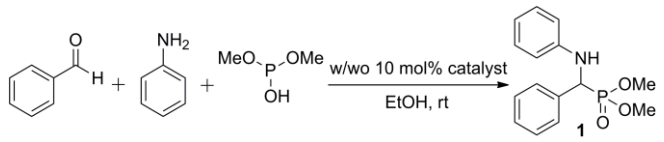
Table 1. The effect of catalyst on the synthesis of α-aminophosphonate **1**



Entry	Catalyst	Reaction time (h)	Isolated yield of **1** (%)
1	--	48	58[a]
2	$Mg(ClO_4)_2$	48	60[a]
3	$ZrOCl_2 \cdot 8H_2O$	12	91
4	$ZrCl_4$	14	90
5	$ZrCp_2Cl_2$	12	92
6	$HfCl_4$	6	98

[a]The reaction was incomplete and quenched at 48 h.

condition finished in only 2 h at room temperature. But the solidification of the reaction system lowered the yield of **1** to 90%. Therefore, 1.0 M appeared to be a proper concentration for the $HfCl_4$-catalyzed reaction.

Table 2. Effect of the amount of $HfCl_4$ on the synthesis of α-aminophosphonate **1**

Entry	Amount of $HfCl_4$ (mol%)	Reaction time (h)	Isolated yield of **1** (%)
1	10	6	98
2	5	8	98
3	2	6	98
4	1	48	82[a]

[a]The reaction was incomplete and quenched at 48 h.

In the following step, we gradually reduced the amount of $HfCl_4$ catalyst from 10 mol% to 1 mol%. As shown in Table 2, the reaction time was prolonged to 8 h without any effect on the yield of **1**, when 5 mol% $HfCl_4$ was used. However, it was surprising to observe that the reaction time was abnormally restored to 6 h, when the amount of $HfCl_4$ was reduced to 2 mol%. However, further decrease the amount of $HfCl_4$ to 1 mol% drastically affected the outcome of the reaction. ^{31}P NMR tracing of the reaction with 2 mol% $HfCl_4$ confirmed the smooth and almost quantitative transformation of dimethylphosphite (δ = 12.3 ppm, $^1J_{P,H}$ = 710 Hz) to α-aminophosphonate **1** (δ = 25.8 ppm) within 6 h.

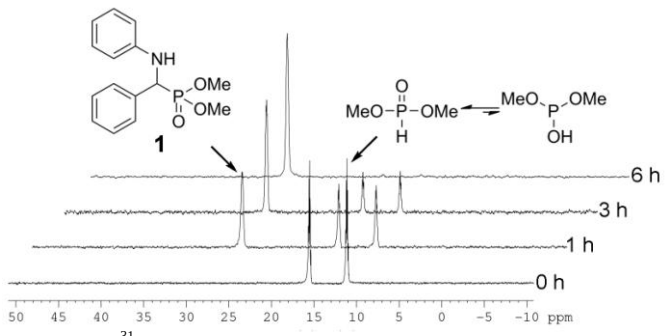


Figure 1. The ^{31}P NMR tracing experiment for the synthesis of **1** with 2 mol% $HfCl_4$ catalyst at room temperature.

As expected, increasing reaction temperature remarkably accelerated the reaction rate (Table 3, entry 1–4). When the reaction with 2 mol% $HfCl_4$ was performed at 60 ºC, the reaction time was shorten to only 30 min without affecting the yield of **1**. Though the reaction finished in 10 min at further elevated temperature (80 ºC), polar byproducts began to show up on TLC plate. The solvent effect was also investigated at 60 ºC (Table 3, entry 5–7). The $HfCl_4$-catalyzed Kabachnik-Fields reaction proceeded with high yield of **1** in dichloroethane (DCE), THF, and CH_3CN, except that longer reaction time was required.

Table 3. The effects of temperature and solvent on the synthesis of α-aminophosphonate **1**

Entry	Temperature (ºC)	Solvent	Reaction time (h)	Isolated yield of **1** (%)
1	20	EtOH	6	98
2	40	EtOH	2.5	98
3	60	EtOH	0.5	98
4	80	EtOH	0.17	90
5	60	DCE	2	97
6	60	THF	3.5	95
7	60	CH_3CN	1	98

With the optimized reaction conditions, a diversity of α-aminophosphonates were synthesized. As shown in Table 4, the reactions with both arylaldehyde and arylamine afforded the corresponding α-aminophosphonates **1**–**10** in excellent yields and completed in 30 min. It is noteworthy that dialkylphosphite and trialkylphosphite resulted in no significant difference in terms of reaction time and yield. In comparison, when alkylaldehydes and/or alkylamines were employed as reactants, longer reaction time (1–2 h) was required and the yields of α-aminophosphonates **11**–**23** were marginally decreased. The application of $HfCl_4$ catalyst for the synthesis of more complicated bis-functionalized alkyldiamines afforded the desired bis-α-aminophosphonates **24**–**27** in 82–87% yields.

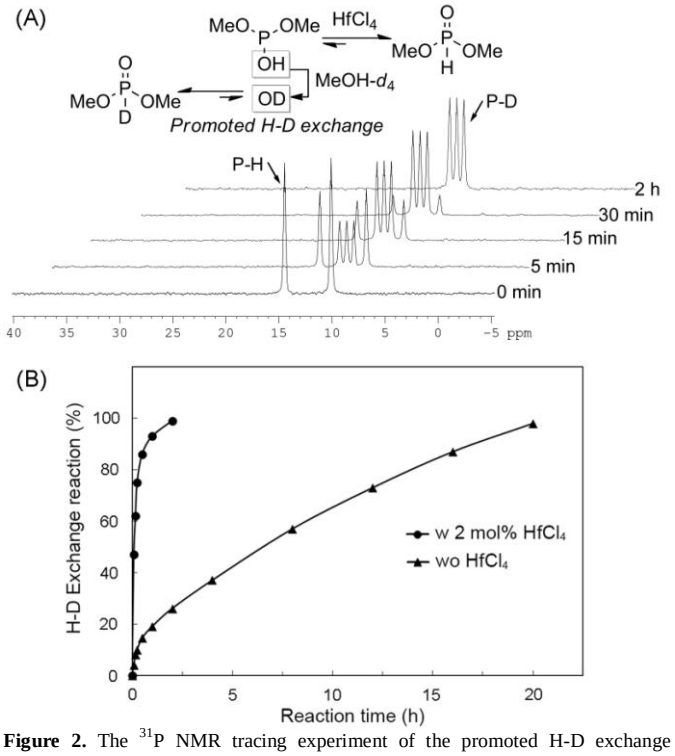
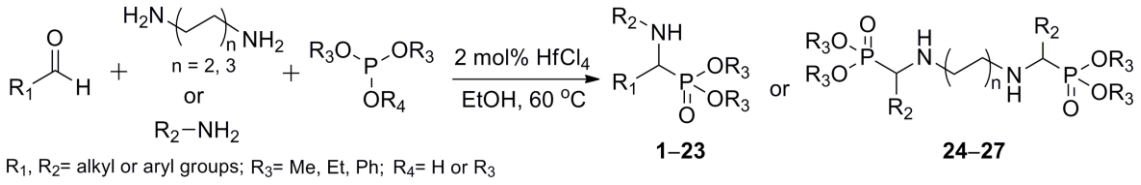
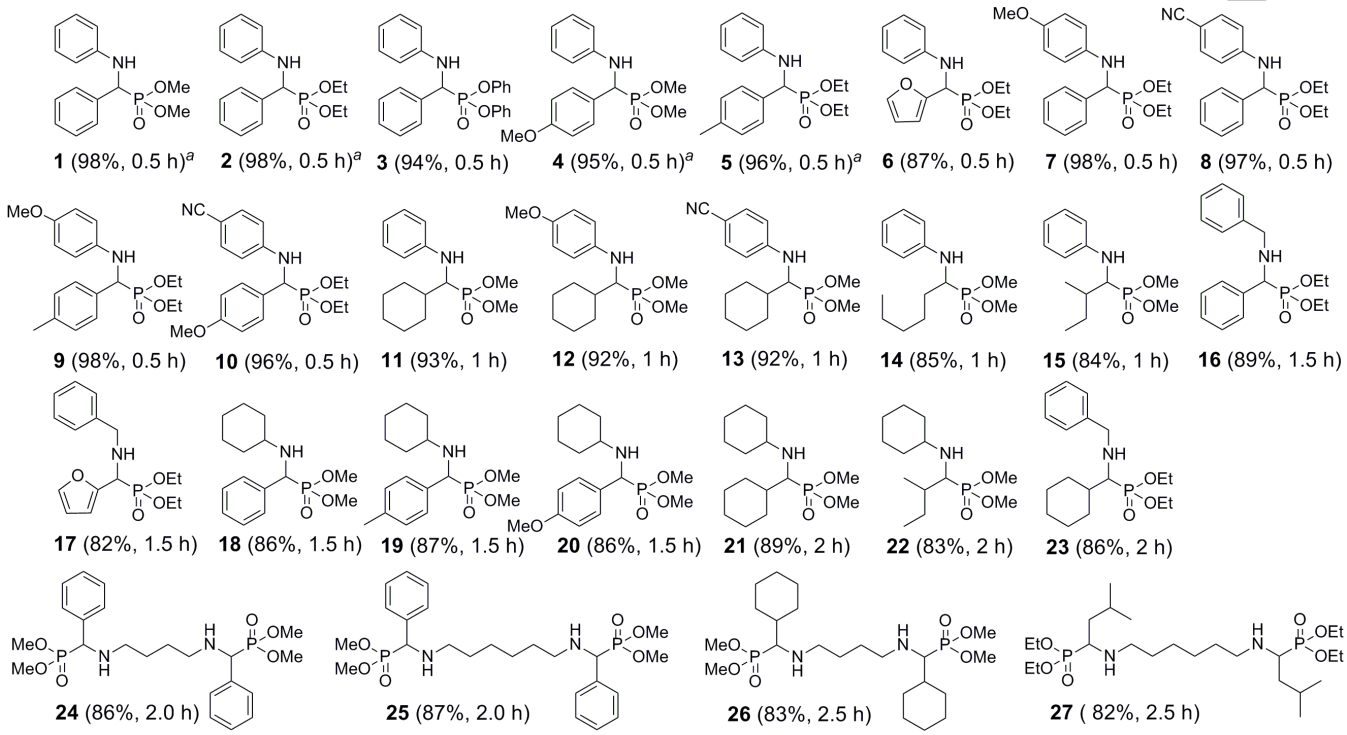


Figure 2. The ^{31}P NMR tracing experiment of the promoted H-D exchange reaction of dimethylphosphite in MeOH-d_4 by 2 mol% $HfCl_4$ (A) and its rate comparison with the control experiment without $HfCl_4$ (B).

Table 4. $HfCl_4$-catalyzed one-pot three-component synthesis of α-aminophosphonates (**1**–**27**)





[a] The reactions with dialkylphosphite and trialkylphosphite showed no difference in terms of yield and reaction time.

It has been proposed that the Kabachnik-Fields reaction proceeded via sequential condensation of aldehyde and amine followed by nucleophilic addition of phosphite to the imine intermediate.[9] However, it has also been proposed that the reaction path may involve the formation of another plausible intermediate, α-hydroxyphosphonate.[17] Our ^{31}P NMR tracing experiment (Figure 1) clearly showed that no peak corresponding to α-hydroxyphosphonate was observed during the entire reaction process. In the control experiment with benzaldehyde, dimethylphosphite, and 2 mol% $HfCl_4$, no reaction was observed.

To clarify the catalytic roles of $HfCl_4$ on the one-pot three-component reaction, we utilized ^{31}P and ^{1}H NMR to examine the interactions of $HfCl_4$ with the individual reactants and imine intermediate. ^{1}H NMR data showed that addition of 2 mol% $HfCl_4$ promoted the conversion of benzaldehyde to the dimethyl acetal within 3 min in MeOH-d_4, indicating the strong effect of Hf(IV) on the activation of aldehyde. Similarly, Hf(IV)-catalyzed fast conversion of benzaldehyde to the corresponding imine in the presence of aniline was observed within 3 min. In comparison, complete formation of imine without $HfCl_4$ catalyst required about 15–20 min. In contrast, the shifts of aniline proton signals upon addition of 2 mol% $HfCl_4$ were negligible. The ^{31}P NMR peaks of dimethylphosphite alone in MeOH showed no difference at all before and after the addition of 2 mol% of $HfCl_4$. Interestingly, when 2 mol% of $HfCl_4$ was added to dimethylphosphite in MeOH-d_4, the proton-deuterium exchange reaction was drastically promoted.[18] As shown in Figure 2A, 99% of P–H (doublet, δ = 12.3 ppm, $^{1}J_{P,H}$ = 710 Hz) was converted to P–D (triplet, δ = 11.8 ppm, $^{1}J_{P,D}$ = 109 Hz) in 2 h. In the control experiment, it took 20 h for the proton-deuterium exchange reaction to reach the same extent (Figure 2B). These results suggested that Hf(IV) accelerated the tautomerization rate between the inactive *H*-phosphonate and reactive phosphite forms,[19] thereby contributing to the overall promotion of the Kabachnik-Fields reaction.

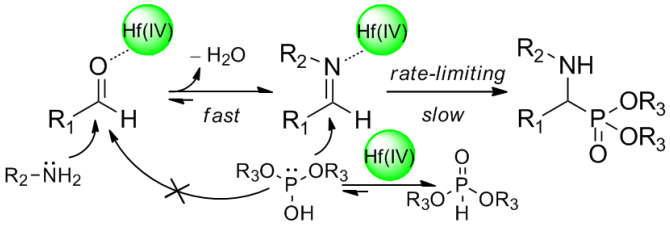


Figure 3. The triple activation roles of Hf(IV) on the formation of α-aminophosphonates in the one-pot three-component reaction.

In the following research, we treated the isolated imine with dimethylphosphite in MeOH and monitored the reaction with ^{31}P NMR. The two-component reaction was as sluggish as the one-pot three-component reaction (Table 1, entry 1). However, addition of 2 mol% $HfCl_4$ drastically accelerated the reaction rate, suggesting that the nucleophilic addition of phosphite to the imine is the rate-limiting step and Hf(IV) also plays an important role on the activation of the imine intermediate. It is worth mentioning that when the isolated imine alone was treated with 10 mol% $HfCl_4$, about 15% of the imine was converted to benzaldehyde dimethyl acetal in MeOH-d_4 when equilibrium was

reached. In contrast, 2 mol% $HfCl_4$ caused no shift from the imine back to the acetyl. These results indicated that less amount of $HfCl_4$ catalyst favored the equilibrium of the imine intermediate, which may compensate the for reaction rate loss due to the lowered amount of catalyst. On the basis of the above results, the mechanism of the $HfCl_4$-catalyzed Kabachnik-Fields reaction is proposed in Figure 3.

In summary, we have developed a highly efficient protocol for the $HfCl_4$-catalyzed synthesis of a variety of α-amino-phosphonates via the one-pot three-component reaction of aldehyde, amine, and phosphite in organic solvents. The experimental data showed that the catalytic activity of $HfCl_4$ is superior to that of the reported Zr(IV) salts in terms of reaction rate, product yield, and amount needed. In addition, the strong NMR evidence elucidated the triple roles of Hf(IV) on the activation of aldehyde, phosphite, and imine intermediate.

Acknowledgments

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Supplementary Material

Supplementary data (experimental procedures, characterization data, and NMR spectra of new compounds) associated with this article can be found at

Graphical Abstract

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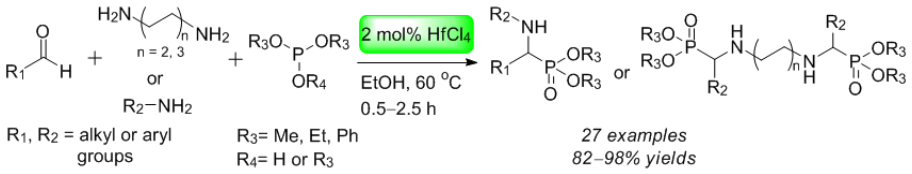

Highlights：

- $HfCl_4$-catalyzed efficient synthesis of α-aminophosphonates has been developed.
- The catalytic activity of $HfCl_4$ is superior to that of the reported Zr(IV) salts.
- The triple catalytic roles of Hf(IV) were elucidated by strong NMR evidence.