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Report

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Lewis Acid Enables Ketone Phosphorylation: Synthesis of Alkenyl Phosphonates

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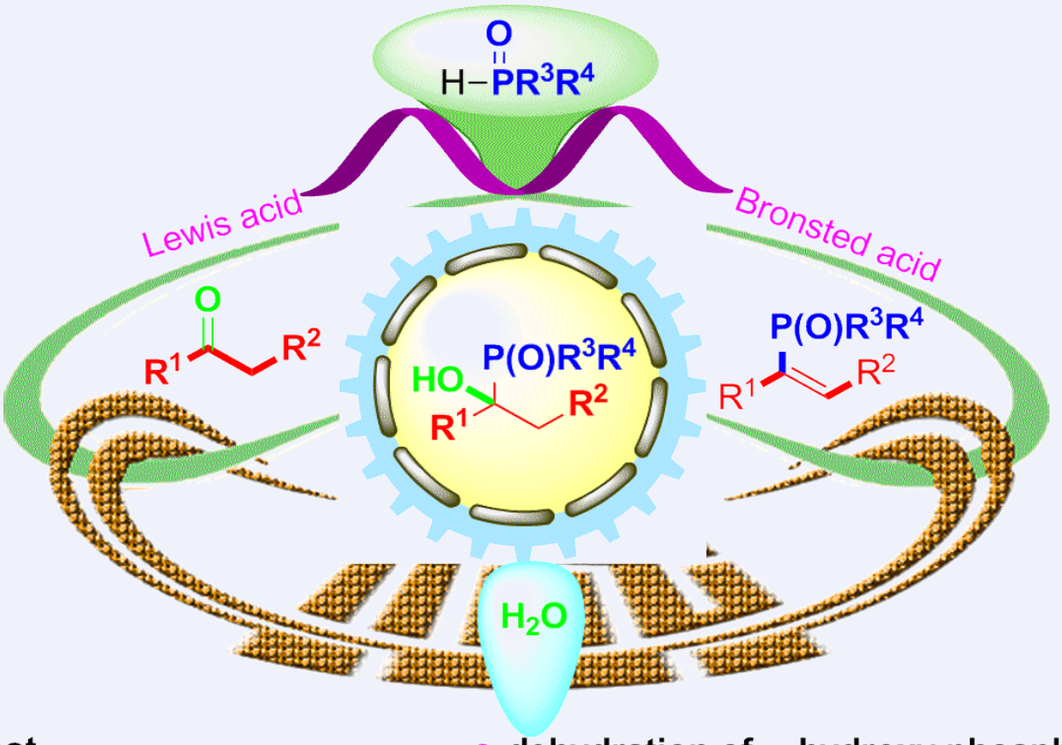
Keywords

Ketone | Phosphorylation | Alkenyl Phosphonates | Lewis Acid | Cascade Reaction

Main observation and conclusion

An efficient Lewis acid enabled ketones phosphonylation to synthesis vinylphosphonates has been developed. This method relays on ketone hydrophosphonylation/α-hydroxy phosphonates unimolecular elimination (E1) dehydration cascade reaction sequence. Various of C-P bond formation product were obtained in moderate to excellent yields with the water as the only byproduct in the reaction.

Comprehensive Graphic Content



- one pot
- easily available and inexpensive
- dehydration of α-hydroxy phosphonates
- addition-elimination cascade reactions

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Background and Originality Content

Organophosphonate compounds and their derivatives play important role in medicinal and material chemistry due to their unique biological and chemical activities.[1] In particular, dialkyl phosphonates exhibit a broad spectrum of significant biological activities (Figure 1).[2] In addition, phosphonates have also wide application in synthetic chemistry, for example, as key reagent in the stereoselective olefination process via Horner-Wadsworth-Emmons reactions, or serve as chiral auxiliaries to provide enantioselective control in the reaction.[3] Among them, vinylphosphonate compounds have shown exceptional application: they can be easily converted into chiral phosphonates by well developed asymmetric hydrogenation;[4] they are crucial building blocks and important synthetic intermediates in the construction of functional-phosphorus compounds,[5] such as aminophosphonic acids[5a-d] and poly(vinylphosphonates);[5e] As a result, the development of efficient methods toward vinylphosphonates compounds have gained significant attention.[6]

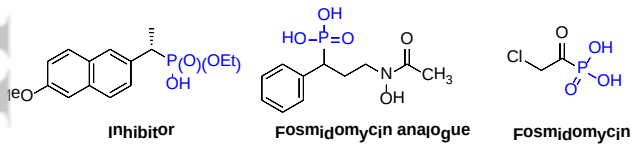
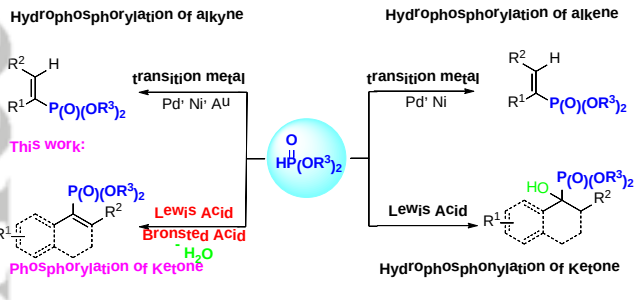


Figure 1 Phosphonate antibiotics.

The most widely used approach in the area is metal-catalyzed coupling of P(O)H compounds with activated vinyl substrates, including vinyl boronophosphonates,[7] halogen,[8] sulfonate,[9] phosphite ester[6i] or α-stannylated vinylphosphonates,[10] and others[11] (Scheme 1). However, these materials were neither easily available nor environmentally friendly. Recently, Han's group developed a highly efficient route to synthesize vinylphosphonate compounds via palladium-catalyzed addition reaction of P(O)H compounds to alkynes reaction (Scheme 1).[6d, 12] However, only moderate efficiency was achieved in regio- and stereo-selectivity control from their study. Feng's group[13]developed a highly efficient synthesis of α-hydroxy

Scheme 1 Synthesis of vinylphosphonates compounds.



phosphonates via Lewis acid-catalyzed hydrophosphonylation of ketones with dimethyl phosphonate, which method was highly tolerable for functionalized ketones (Scheme 1). Herein, we disclose a general and efficient method for the synthesis of vinylphosphonate compounds from ketones with dialkyl phosphate, via ketone hydrophosphonylation/α-hydroxy phosphonates unimolecular elimination (E1) dehydration cascade reaction sequence. The method benefits from using cheap and easily available materials, and rea lized in an environmentally friendly and atomic economy way with the water as the only by-product (Scheme 1).

Results and Discussion

Table 1 Optimization of the reaction conditions

Entry	Catalyst	Additive	Solvent	Yield(%)[a, b]
1	AgOTf		DCE	50%
2	AgTFA		DCE	trace
3	$AgNO_3$		DCE	trace
4	AgOTf		CH_3CN	NR
5	AgOTf		CH_3Ph	32%
6	AgOTf		THF	trace
7	AgOTf	HOAc	DCE	40%
8	AgOTf	PivOH	DCE	41%
9	AgOTf	TsOH	DCE	15%
10	AgOTf	CF_3COOH	DCE	32%
11	AgOTf	Tf_2O	DCE	70%
12	**AgOTf**	**HOTf**	**DCE**	**84%**
13[c]	AgOTf	HOTf	DCE	60%
14[d]	AgOTf	HOTf	DCE	73%
15	$Ni(OTf)_2$	HOTf	DCE	50%
16	$Al(OTf)_3$	HOTf	DCE	52%
17	$Fe(OTf)_2$	HOTf	DCE	53%
18	$Mg(OTf)_2$	HOTf	DCE	51%
19	$Ti(O\textit{i}Pr)_4$	HOTf	DCE	64%
20[e]	AgOTf	HOTf	DCE	80%
21		HOTf	DCE	37%

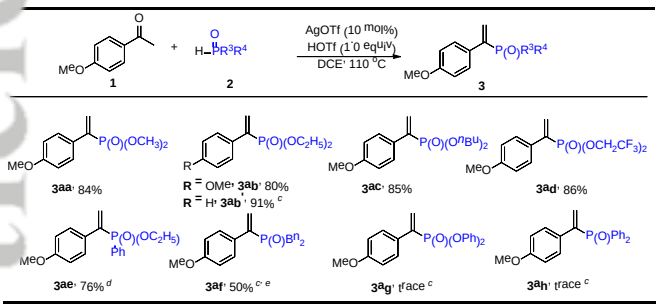
[a] Reaction conditions: **1a** (0.1 mmol), dimethyl phosphonate (2.5 equiv), catalyst (0.1 equiv), additive (1 equiv), solvent (1 mL) , 110 °C, air, 15 h. [b] Isolated yield by column chromatography. [c] HOTf (0.5 equiv). [d] HOTf (1.5 equiv). [e] argon conditions

In the initial study, we used the 1-(4-methoxyphenyl)ethanone **1a** and dimethyl phosphonate **2a** as the model substrates and firstly tested different silver salts as the Lewis acid catalyst in reaction (Table 1, entries 1-3, see supporting information for details). To our delight, the desired vinylphosphonate product **3aa** was obtained in 50% yield by using AgOTf as catalyst (Table 1, entry 1). Meanwhile, different solvents screening indicated that DCE was the best choice (Table 1, entries 4-6). Next, we believed that the acid additives should play a key role in the reaction, so we further screening acid additives. It was found that HOTf was the best choice, affording the desired product **3aa** in 84% yield (Table 1, entries 7-12). When the reaction temperature was increased to 120 °C or decreased to 100 °C, the yield of **3aa** decreased to some extent (Table 1, entries 13-14). We also applied other Lewis acid in the reaction, Although all of them can catalyzed the reaction, AgOTf was still the better catalyst under the condition (Table 1, entries 15-19). Running the reaction under the argon atmosphere provided no enhancement to the reaction (Table 1, entry 20). Finally, the control experiment showed a very low efficient were achieved in the absence of AgOTf catalyst (Table 1, entry 21). Thus, the standard reaction conditions was obtained: AgOTf (10 mol%) as the catalyst, 1.0 equiv HOTf as additive, in 2.0 mL DCE for 0.3 mmol 1-(4-methoxyphenyl)ethanone **1a** with 2.5 equiv dimethyl phosphonate **2a**, at 110 °C under an air atmosphere.

With the optimal reaction conditions in hand, we then examined the substrate scope of the reaction. The summary of 1-(4-methoxyphenyl)ethanone **1a** reacted with different P-sources as shown in Scheme 2. The catalytic system worked well with hydrogen phosphonates such as dimethyl phosphonate, diethyl

phosphonate, dibutyl phosphonate and bis(2,2,2-trifluoroethyl)phosphonate (**2aa**-**2ad**), ethyl phenylphosphinate **2e** to give the desired products in moderate yield. Clearly, dialkyl phosphonate substrates showed a significant higher activity compared with the diphenyl phosphate and phosphine oxides substrates under standard condition (**3ag**-**3ah**). The other reason may be that the electrophilic phosphorus species formed by diphenylphosphine oxide in the presence of Tf_2O or HOTf, which was inhibited the reaction.[14]

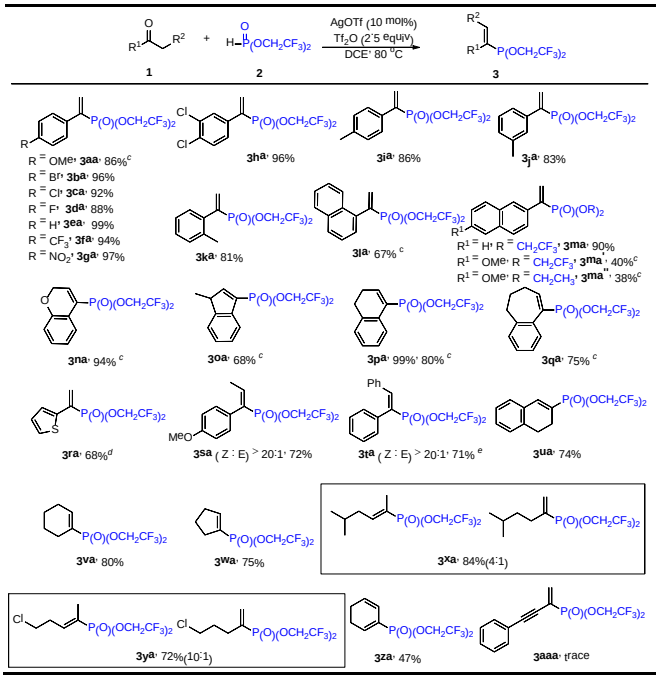
Scheme 2 Substrate scope of P-sources [a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2** (2.5 equiv), AgOTf (10 mol%), and HOTf (1.0 equiv) was stirred in DCE (3 mL) at 110°C under air for 15 h. [b] Yield of the isolated product. [c] Tf_2O (2.5 equiv), 80 °C. [d] 24 h. [e] 24 h.

We next surveyed the scope of ketone component with bis (2,2,2-trifluoroethyl) phosphonate **3d** (Scheme 3). Only 45% yeild the desired product was obtained when 1-(4-bromophenyl)ethanone was introduced the optimized condition. We further screened the reaction conditions and found that when 1.0 equiv of HOTf was replaced by 2.5 equiv of Tf_2O, the yield of the product increased up to 96% yeild and the reaction temperature was decreased to 80 °C (see supporting information for details). And then we investagated different substituent on the phenyl ring of acetophenone, to our delight, both electron-withdrawing or electron-donating groups were tolerated well under condition and delivered the desired product in excellent yields (Scheme 3, entries **3ba**-**3ia**). At the same time, strong electron withdrawing groups on the phenyl ring of acetophenone can also obtain excellent yields, such as CF_3 and NO_2 (Scheme 3, entries **3fa**-**3ga**). Also, the steric effect of the substitution have a minimal effect on the outcome of the reaction, **3ia**-**3ka** were obtained in a similar yield compared with parent substrate. In addition, 1-acetonaphthone and 2-acetonaphthone could also provide the vinylphosphonate product **3la**-**3ma** in 67%-90% yields. However, the corresponding products **3ma**'-**3ma**'' were obtained in moderate yields when 1-(6-methoxynaphthalen-2-yl)ethanone was introduced under reaction condition. Furthermore, chroman-4-one was introduced to the optimization of reaction conditions and corresponding vinylphosphonate **3ha** was obtained in an excellent yield (94% yield). At the same time, other benzene fused cyclic ketones **1o**-**1q** could also reacted with bis (2,2,2-trifluoroethyl) phosphonate to deliver the desired product in moderate to excellent yields (Scheme 3, entries **3oa**-**3qa**). Moreover, we found that heteroaromatic ketone can be successfully converted into corresponding product **3ra** at a much lower temperature. To our delight, compared with HOTf as additive, when 1-(4-methoxyphenyl)-2-phenylethanone **1s**, 1,2- diphenylethanone **1t** and 3,4-dihydronaphthalen-2(1H)-one **1u** were applied under Tf_2O reaction conditions, the desired product **3sa**, **3ta** and **3ua** were obtained in 71%-74% yields with a highly chemo-selective in the system. What's more, others substituted aliphatic ketones, such as cyclic ketones, straight chain aliphatic ketones and conjugated ketones, could also generate the desired product in moderate to high yields with highly stereo-selectivity (Scheme 3, entries **3va**-**3za**). However, the results show that the regioselectivity of the product competes with the hydrogen phosphorylation on C=C bond and C=O bond when cyclohex-2-enone was introduced into reaction under the optimized reaction conditions. Unfortunately, only trace product were obtained when 4- phenylbut-3-yn-2-one was introduced to optimized reaction conditions (Scheme 3, entry **3aaa**).

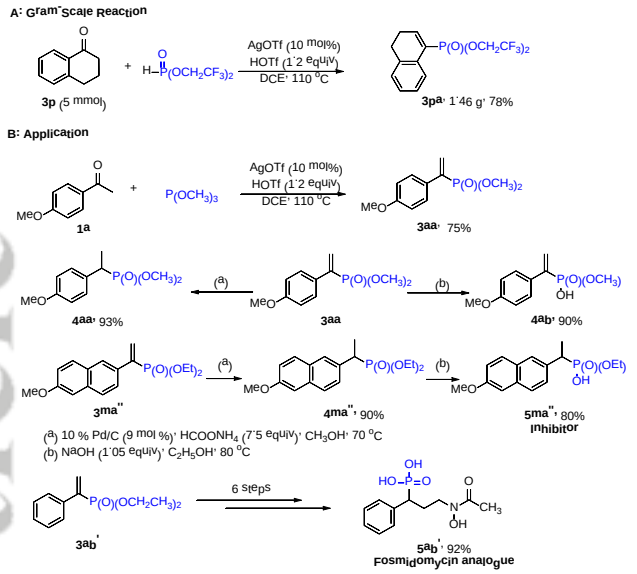
Scheme 3 Substrate scope of ketones [a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2** (2.5 equiv), AgOTf (10 mol%), and Tf_2O (2.5 equiv) was stirred in DCE (3 mL) at 80°C under air for 15 h. [b] Yield of the isolated product. [c] HOTf (1.0 equiv), 110 °C. [d] HOTf (1.0 equiv), 60 °C. [e] $Al(OTf)_3$ (10 mol%).

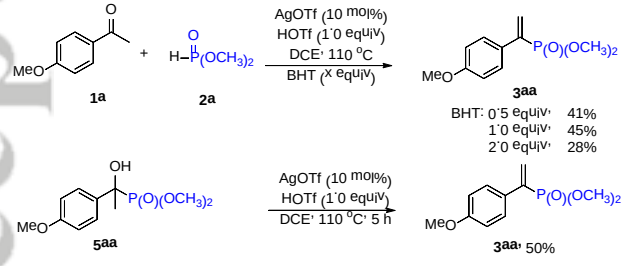
In order to demonstrate the utility of our reaction, firstly, we tested a large-scale experiment with 5 mmol **3p** was used under the standard reaction conditions, to our delight, 1.46 g of the corresponding product **3pa** was obtained in the reaction without siginificant decrease in the yield (**A**, Scheme 4). In addition, **3aa** was obtained in 75% yield from **1a** with trimethyl phosphate under the optimal reaction conditions. Meanwhile, we also demonstrated that the products of our system could be easily converted into other derivatives. For example, compound **4aa** and **3ma**''could be easily obtained in 93% yield through facile reduction of the **3aa**.[9b] At the same time, inhibitor **5ma**'' is an important non-steriod anti-flammatory precursors of drug, which was synthesized from easily available material, 1-(6-methoxynaphthalen-2-yl)ethanone **2m** (**B**, Scheme 4).[2f] Moreover, α-arylphosphonates derivatives are widely used because of their interesting biological properties. It has been proven that Fosmidomycin analogue **5ab**' could result in marked increase in the antimalarial activities (**B**, Scheme 4). We found that **3ab**' can be successfully converted into corresponding product Fosmidomycin analogue **5ab**' in 92% yield.[15]

Scheme 4 Gram-scale reaction and application.

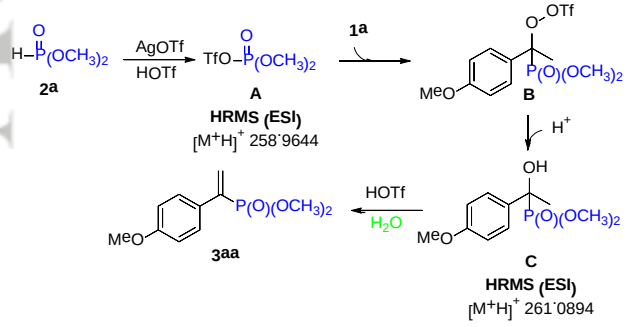


To investigate the mechanism of this transformation, the control experiments were carried out. First, when 2.0 equiv of 2,6-di-tert-butyl-4-methylphenol (BHT) was added in standard reaction conditions, only 28% of the desired product **3aa** was observed (84 % under standard condition), this demonstrated that the radical process might not be involved in this system (Scheme 5). Subsequently, when dimethyl (1-hydroxy-1-(4-methoxyphenyl)ethyl) phosphonate **5aa** was introduced under standard condition, the desired product **3aa** was detected in 50% yield. This result suggests that dimethyl (1-hydroxy-1-(4-methoxyphenyl)ethyl) phosphonate **5aa** may be the key intermediate in the reaction (Scheme 5).

Scheme 5 Mechanism of the control experiments.



Scheme 6 Proposed mechanism.



A plausible mechanism is proposed on the basis of our control experiments and previous works (Scheme 6).[16] Initially, dimethyl phosphonate **2a** to form the intermediate **A** under the HOTf and AgOTf system, which was detected by insitu HRMS (see supporting information),[16b, 16c] then intermediate **A** was added to 1-(4-methoxyphenyl)ethanone **1a** to generate intermediate **B.** Subsequently intermediate **C** was obtained following facile dissociation in the presence of H^+,[16a, 16d, 16e] which was also detected by insitu HRMS (see supporting information). Finally, the product **3aa** was obtained through the unimolecular elimination (E1) dehydration of **C** (Scheme 6).

Conclusions

In summary, we have achieved first example of synthesis of vinylphosphonate from ketones and dialkyl phosphite. Mechanistically, the reaction goes through a Lewis acid promoted ketone hydrophosphonylation/α-hydroxy phosphonates unimolecular elimination (E1) dehydration cascade reaction sequence relying on the advantages of starting from cheap and easily available substrates, as well as producing water as the only byproduct. A series of vinylphosphonate derivates were synthesized in moderate to excellent yields.

Experimental

General procedure for the synthesis of vinylphosphonates

General procedure A: An oven-dried 10 mL screw-capped vial containing **1a** (0.3 mmol, 1.0 equiv), AgOTf (0.03 mmol, 0.1 equiv), and DCE (3 mL) was added *via* syringe, dimethyl phosphate (0.75 mmol, 2.5 equiv), HOTf (0.3 mmol, 1.0 equiv), and then heated to 110 °C in an oil bath until the starting material has disappeared for 15 hours (monitored by TLC). And then the solvent was removed in vacuo and residue was purified was purified by column chromatography on a short silica gel column using EA/PE as eluent to afford the desired product **3**.

General procedure B: An oven-dried 10 mL screw-capped vial containing **1a** (0.3 mmol, 1.0 equiv), AgOTf (0.03 mmol, 0.1 equiv), and DCE (3 mL) was added *via* syringe, bis (2,2,2-trifluoroethyl) phosphonate (0.75 mmol, 2.5 equiv), Tf_2O (0.75 mmol, 2.5 equiv), and then heated to 80 °C in an oil bath until the starting material has disappeared for 15 hours (monitored by TLC). And then the solvent was removed in vacuo and residue was purified was purified by column chromatography on a short silica gel column using EA/PE as eluent to afford the desired product **3**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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Lewis Acid Enables Ketone Phosphorylation: Synthesis of Alkenyl Phosphonates

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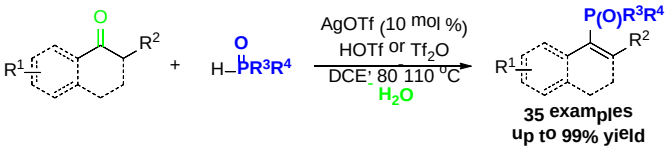

A Lewis acid catalyzed cascade reaction of ketone phosphorylation has been developed that enables synthesis of vinylphosphonate derivates in moderate to excellent yields.

