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Markovnikov-addition of H-phosphonates to terminal alkynes under metal- and solvent-free conditions†

Nana Xin, *[a] Yongjian Lian,[a] Yongzheng Lv,[a] Yongjie Wang,[b] Xian-Qiang Huang[a] and Chang-Qiu Zhao *[a]

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An addition of H-phosphonates to aryl alkynes was realized under solvent- and metal-free conditions, affording Markovnikov-selective α-vinylphosphonates in moderate to good yields. A wide range of aryl alkynes could be applied for the reaction. A tentative mechanism of addition–substitution was proposed based on *in situ* $^{31}P\{^{1}H\}$ NMR studies.

Vinyl phosphorus compounds are of high importance because of their wide application in the fields of biological metabolism,[1] functional materials,[2] and as synthetic blocks of organophosphorus compounds.[3] Some reviews have documented the preparations and applications of the vinyl phosphorus.[4] Normally, the compounds can be acquired from alkynes, *via* the addition with H–P species. Aromatic ketones and aldehydes are also used as the sources of vinyl phosphorus, *via* multi-step conversions.[1b,5] The recently developed methods to obtain vinyl phosphorus involving H–P species include decarboxylation of cinnamic acid,[6] dehydrogenation of active alkene,[7] and dehydration of alcohols.[8]

The addition of H–P species to alkynes is undoubtedly the most effective and atom economical method. The addition was usually catalysed by metals.[4e,9] One of the authors has reported palladium and rhodium catalysed additions of H–P species to alkynes.[9a–d] Similar additions could be realized by catalysis with copper, nickel, molybdenum and ytterbium (Chart 1).[10] The metal-catalysed procedures also include Suzuki reaction and others.[11] Although much progress has been made in this area, problems associated with narrow substrate scope, the need to use expensive transition metals and a stoichiometric amount of additives, and poor regio- and stereo-control have encouraged researchers to search for new and more efficient methods.

Recently, triflic anhydride (Tf_2O) has been applied for electrophilic activation of amides and P=O species, and the activated intermediates could be used for the substitutions with various nucleophilic reagents.[7b,12] The conversions of P=O species to C(sp^2)–P bonds are quite rare. Miura and coauthors have reported a Tf_2O promoted activation of secondary phosphine oxides, which is applied for phosphination and intramolecular cyclization with alkynes.[13] However, the scopes are limited with inner-alkynes. The application of H-phosphonates was not reported for the reaction (Chart 1).

Herein we enclosed a novel Tf_2O promoted reaction of terminal alkyne with H-phosphonates. Vinyl phosphonates were afforded under metal- and solvent-free conditions, in excellent Markovnikov-regio selectivity.

Phenylacetylene (**1a**) was initially treated with diethyl phosphite (**2a**) in the presence of Tf_2O in a molar ratio of 1 : 1 : 1. To

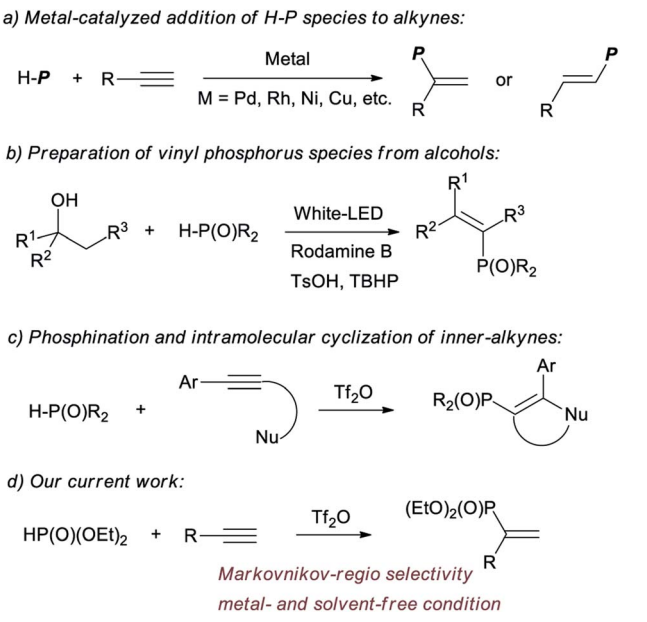

Chart 1 Comparison of the construction of C(sp^2)–P bonds to our current work.

[a]*Institution of Functional Organic Molecules and Materials, Shandong Provincial Key Laboratory of Chemical Energy Storage and Novel Cell Technology, Liaocheng University, College of Chemistry and Chemical Engineering, Liaocheng, Shandong 252059, China. E-mail: xinnana2008@163.com; literabc@hotmail.com*

[b]*Liaocheng Power Supply Company, Liaocheng, Shandong 252059, China*

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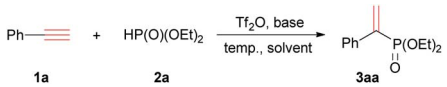
Table 1 Optimization of reaction conditions[a]



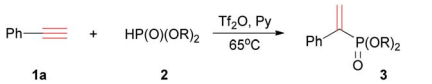
Entry	Molar ratio of **1a**/**2a**/Cat	Base	Temp.	Solvent (1 mL)	Conversion% (isolated yield%)[b]
1	1 : 2 : 1	—	Rt	—	12
2	1 : 2 : 1	—	40 °C	—	46
3	1 : 2 : 1	—	60 °C	—	92
4	1 : 2 : 1	—	65 °C	—	98 (53)
5	1 : 2 : 1	—	80 °C	—	98 (56)
6	1 : 2 : 0.5	—	65 °C	—	79
7	1 : 2 : 0.8	—	65 °C	—	92
8	1 : 2 : 1.2	—	65 °C	—	86
9	1 : 2 : 1	—	65 °C	—	0[c]
10	1 : 2 : 1	—	65 °C	CH_2Cl_2	3
11	1 : 2 : 1	—	65 °C	Toluene	9
12	1 : 2 : 1	—	65 °C	THF	0
13	1 : 2 : 1	—	65 °C	EtOAc	22
14	1 : 2 : 1	Na_2CO_3	65 °C	—	0[d]
15	1 : 2 : 1	Pyridine	65 °C	—	99 (64)[d]
16	1 : 2 : 1	2,6-Lutidine	65 °C	—	99 (54)[d]
17	1 : 2 : 1	DBU	65 °C	—	99 (64)[d]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.40 mmol) and Tf_2O (0.2 mmol) stirring at different temperatures for 24 h. [b] The conversions were estimated based on ^1H NMR spectrum, and isolated yields were calculated based on **1a**. [c] TfOH was used. [d] 1.0 equiv. of base was used.

our delight, diethyl 1-phenyl ethenylphosphonate (**3aa**), a Markovnikov addition product, was obtained in high regioselectivity but in poor yield (10%). The reaction conditions were subsequently optimized with **1a** and **2a**. Considering Tf_2O was moisture sensitive, all experiments were performed under nitrogen. Two equivalents **2a** was used to ensure **1a** was consumed as much as possible. The conversion and isolated yield were calculated based on **1a** (Table 1).

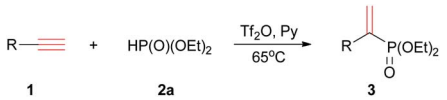
When the mixture of **1a**, **2a** and Tf_2O was stirred at room temperature, a new signal at 17.1 ppm was observed on ^{31}P NMR spectrum. The two doublet peaks at 6.35 and 6.17 ppm on proton NMR spectrum, assigned as **3aa**, was detected in 12% (entry 1 of Table 1). The conversion of **1a** was improved to 46% when the reaction was carried out at 40 °C, and to 92% at 60 °C (entries 2 and 3). At 65 °C, the conversion was detected in 98%, and **3aa** was isolated, whose structure was confirmed by NMR

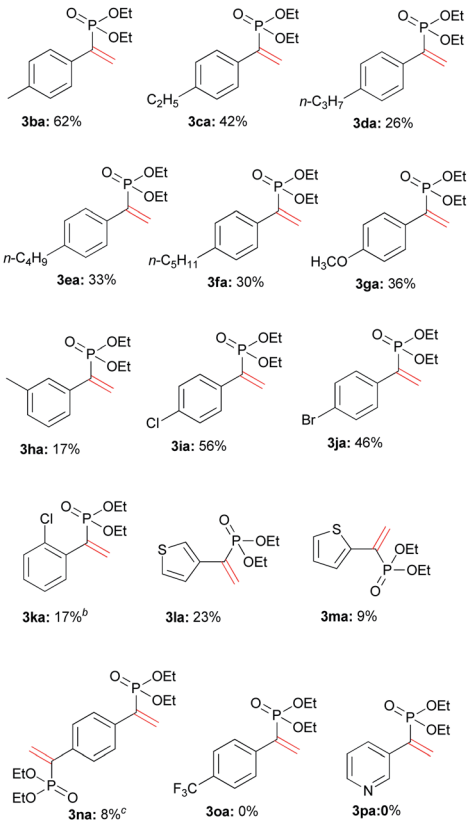
Table 2 Reactivity of phenylacetylene and H-phosphonates



[a] Isolated yields based on **1a**.

Table 3 Scope of alkynes[a]





[a] Isolated yield. [b] Two equivalents of Tf_2O were used. [c] The alkyne/P–H regent/Tf_2O/pyridine were used in the molar ratio of 1 : 4 : 2 : 2.

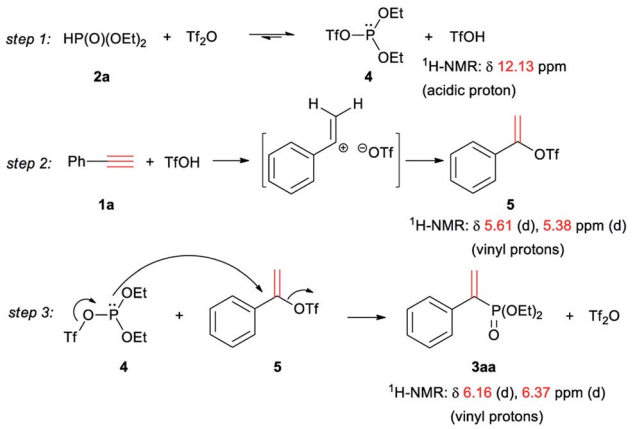
spectrum.[14] The conversion cannot be further improved at higher temperature such as 80 °C.

When 0.5 equiv. Tf_2O was used, the conversion of **1a** was dropped to 79%. The usage of 0.8 equivalent of Tf_2O led 92% conversion (entries 6 and 7). However, excessive Tf_2O, such as 1.2 equivalents, resulted in the reduced conversion (86%, entry 8).

Once triflic acid was used to replace Tf_2O, **3aa** was not detected (entry 9).

To carry the reaction in some solvent such as dichloromethane, toluene, THF or ethyl acetate, gave worse result than neat condition (entries 10–13). In the presence of sodium carbonate, the reaction cannot take place (entry 14). The presence of pyridine, 2,6-lutidine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) slightly increased the conversion (entries 15–17).

Adopting the above optimized condition, the reaction of alkyne with H-phosphonate was performed (Table 2). Dimethyl phosphite **2b** reacted with phenylacetylene to afford dimethyl 1-phenylethenyl phosphonate **3ab** in 43% yield, which was less than the reaction of **2a**. Perhaps due to the bigger spatial hindrance, diisopropyl phosphite **2c** did not reacted with **1a** to



Scheme 1 Proposed mechanism.

afford **3ac**. The reactions of diphenylphosphine oxide or ethyl phenylphosphinate cannot occur.

Various terminal alkynes was then examined (Table 3). Besides of **1a**, aromatic alkynes possessing electron-donating groups smoothly reacted with **2a** to afford corresponding **3ba**–**3ha** in 17–62% yields. The low yield of **3ha** may be ascribed to *meta*-methyl that had variable electronic effect. For chloro and bromo-substituted alkynes, **3ia** and **3ja** were afforded in 56% and 46% yields, respectively. Perhaps due to steric hindrance, the *ortho*-chlorophenyl ethyne gave lower yield of **3** than *para*-substituted alkyne.

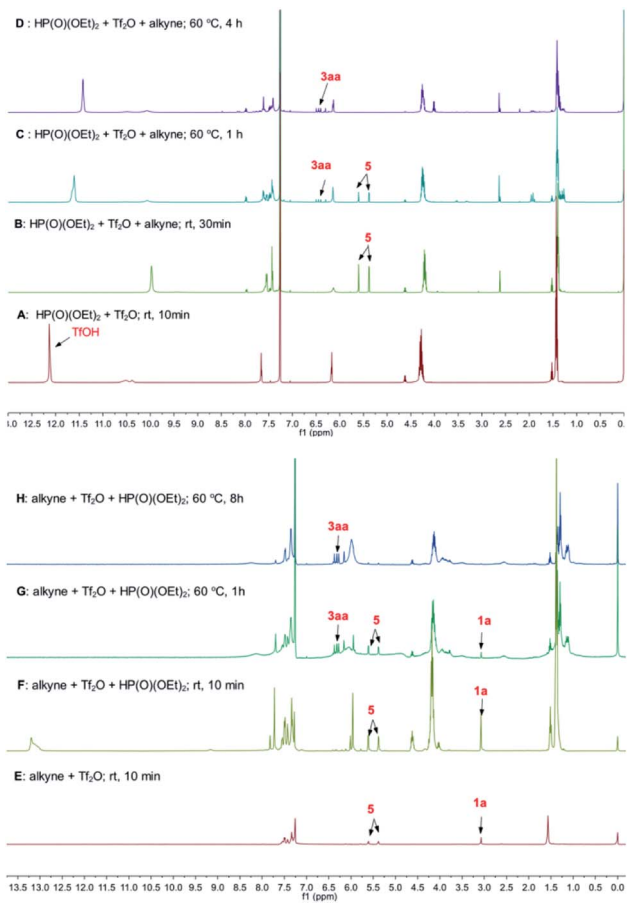


Fig. 1 The results of *in situ* NMR experiments of the reaction of **1a** with **2a** in the presence of triflic anhydride.

Some ethynyl heterocycles, such as 2- or 3-ethynylthiophene could be employed for the reaction, affording **3la** or **3ma**, respectively. For 1,4-diethynylbenzene (**1n**), the addition was realized when **2a** and Tf_2O were used in double equivalents. However, the alkynes having strong EWG, such as trifluoromethyl or 3-pyridinyl, cannot react with **2a**. Aliphatic terminal alkynes, such as 1-octyne, also did not afford the product.

The mechanism of the reaction was studied *via in situ* NMR experiments, and was proposed in Scheme 1. **2a** and Tf_2O formed triflate **4** of phosphite *via* an equilibrium.[12b,15] Meanwhile, triflic acid was generated (step 1). The addition of triflic acid to **1a** formed 1-phenylvinyl triflate **5** as an intermediate (step 2). The subsequent nucleophilic substitution of **5** with **4** formed vinyl phosphonate **3aa** (step 3).

The step 1 was confirmed by the observation of the signal of acidic proton in TfOH during the mixing of **2a** with Tf_2O (Fig. 1A). When **1a** was added, **5** was detected, as seen the two doublet peaks at 5.61 and 5.38 ppm on ^1H NMR spectrum (step 2 and Fig. 1B). When the mixture was heated at 60 °C, the signals of **3aa** at 6.16–6.37 ppm emerged. The peaks were increased with prolonged heating, accompanied with the decreasing of the signals of **5** (step 3, Fig. 1C and D). Similar results were observed when Tf_2O was initially mixed with **1a** (Fig. 1E–H). After heating at 60 °C for 8 h, the signals of **1a**, respected by the peak of terminal alkyne at 3.07 ppm, were disappeared (Fig. 1H).

The addition of triflic acid to **1a** probably formed α-carbon ion as intermediate, which could be stabilized by phenyl and be converted to Markovnikov-product **5**. Although the nucleophilic substitution on vinyl carbon was difficulty, the strong leaving activity of trifluoromethanesulfonyloxy on **5** enabled step 3 occurred. Miura proposed a cyclic phosphirenium intermediate for the addition and cyclization,[13] which could be probably stabilized by the alkyl groups of inner-alkynes and secondary phosphine oxides. In our case, the electron-withdrawing alkoxyl on phosphorus of **2a** was not favorable for the formation of the phosphirenium, thus the reaction proceeded *via* α-carbon ion and addition–substitution occurred.

TfOH was necessary to the formation of **5** from **2a** (step 2). However, triflic acid cannot sole promote the reaction, as seen in entry 9 of Table 1. The results indicated the poor nucleophilic ability of **2a**. After **2a** was converted to P(III) species **4** by triflic anhydride, the lone electron pair on phosphorus of **4** could attack **5** to form the product. It was not sure the small quartet peak at 4.62 ppm belonged to **4** (Fig. 1F). On ^{31}P NMR spectrum, the peak of **2a** at 17.0 ppm obviously became broad in poor resolution when mixed with triflic anhydride (as seen in ESI†). The results also supported the equilibrium between **2a** and **4** (step 1).

Conclusions

In summary, a mild and convenient method to generate vinylphosphonates was developed. The method employed aryl

alkynes and H-phosphonates, was performed under metal- and solvent-free conditions, and afforded Markovnikov-adducts as single regio-isomer. This methodology was compatible with a wide range of aryl alkynes. On the basis of *in situ* ^{1}H NMR studies, an addition–substitution mechanism was proposed, which was different to the reported phosphirenium mechanism.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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