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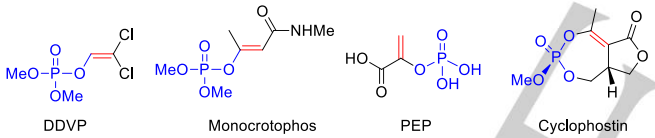
Metal-Free Hydrophosphoryloxylation of Ynamides: Rapid Access to Enol Phosphates

Dalie An,[a] Weinan Zhang,[a] Bin Pan,*,[b] Yingying Zhao*,[a]

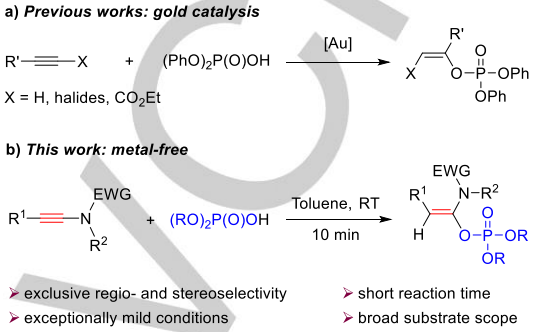
Abstract: We herein report a metal-free hydrophosphoryloxylation of ynamides with phosphoric acids, which provides an expeditious route to access useful enol phosphates. The advantages of this protocol include exclusive selectivity, short reaction time, high efficiency and broad substrate scope. Additionally, the products can serve as good partners in Suzuki-Miyaura cross-coupling.

Enol phosphates are an intriguing class of organophosphates that can be found in a variety of agrochemicals and bioactive natural products.[1] For example (Scheme 1), dimethyl 2,2-dichlorovinylphosphate (DDVP) and monocrotophos are widely used as insecticides in agriculture.[2] Phosphoenolpyruvate (PEP), containing high-energy phosphate bonds, can facilitate the transformation of adenosine diphosphate (ADP) into adenosine triphosphate (ATP) in living organisms.[3] Cyclophostin, isolated from *Streptomyces* strains, exhibits potent inhibition against acetyl cholinesterase (AChE) from the housefly and brown plant hopper.[4] Besides, enol phosphates are also versatile building blocks in transition-metal-catalyzed cross-couplings.[5] Therefore, tremendous efforts have been devoted to the synthesis of such important frameworks over the past decades.



Scheme 1. Representative bioactive molecules containing enol phosphates.

The most commonly used protocol relies on the reaction of carbonyl compounds, such as enolization/phosphorylation,[6] Perkow reaction,[7] and *O*-phosphorylation of unsaturated ketones.[8] Notably, hydrophosphoryloxylation of alkynes represents another efficient strategy. In 2010, Lee and Kim et al developed an elegant gold-catalyzed addition of disubstituted phosphates with terminal alkynes, enabling a facile synthesis of enol phosphates (Scheme 2a).[9] Later, the similar results were observed by Nolan and co-workers.[10] Besides, haloalkynes could also participate in this addition with high regioselectivity (Scheme 2a).[11] Nevertheless, metal-free hydrophosphoryloxylation of alkynes, internal alkynes in particular, has never been reported before, likely due to the difficulty in controlling the regioselectivity.



Scheme 2. Hydrophosphoryloxylation of alkynes with phosphoric acids.

Ynamides are special alkynes that feature the electron-donating nitrogen atom directly attached to the carbon-carbon triple bond, and their high electron density can be finely balanced by the electron-withdrawing substituent on the nitrogen atom. Consequently, ynamides can display diverse reactivities in organic synthesis and their chemistry has become a research hotspot.[12] The recent years have witnessed impressive advances in hydrofunctionalizations of ynamides.[13] For instance, Lam et al[14] and Bi et al[15] achieved the regioselective hydroacyloxylation of ynamides with carboxylic acids under palladium catalysis and metal-free conditions, respectively. Besides, metal-free additions of hydrogen halides[16] and sulfonic acids[17] to ynamides were also well documented. Prompted by these precedents and our continuing interests in ynamide chemistry[18], we envisioned that phosphoric acid might undergo addition with ynamides to yield useful enol phosphates. Indeed, this expected hydrophosphoryloxylation could proceed smoothly with no need of transition-metal promoters, and notably most of the cases could be completed within 10 minutes at room temperature (Scheme 2b). Given that the protocol features excellent regioselectivity, exclusive (*E*)-stereoselectivity, short reaction time, mild conditions, metal-free system, and useful products, we herein present the results of our studies.

At the outset, ynamide **1a** and diphenyl phosphate **2a** were selected as the model substrates to test our hypothesis (Figure 1). To our delight, when a solution of **1a** and **2a** in DCM was stirred at room temperature for 10 min, the expected hydrophosphoryloxylation could occur spontaneously without any catalyst, producing enol phosphate **3a** in a good yield with an exclusive regioselectivity. The effect of other solvents was further surveyed. The reactions in THF and MeCN gave inferior outcomes, while a higher yield of **3a** was obtained in non-polar solvent toluene. The strong polar solvent DMSO totally suppressed the transformation. It is noted that the yield still remained high when the reaction was conducted under air.

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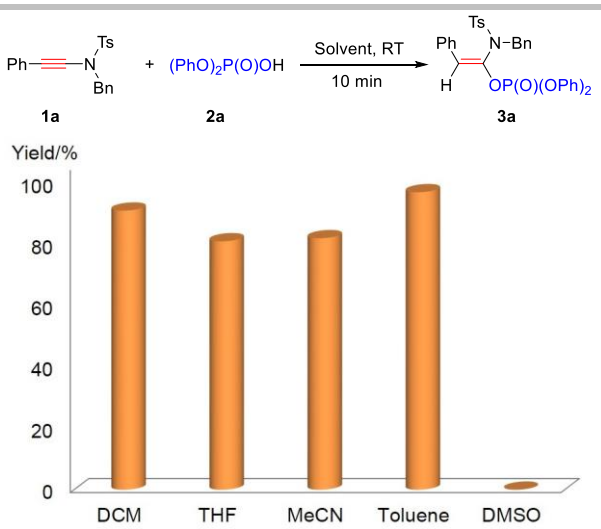
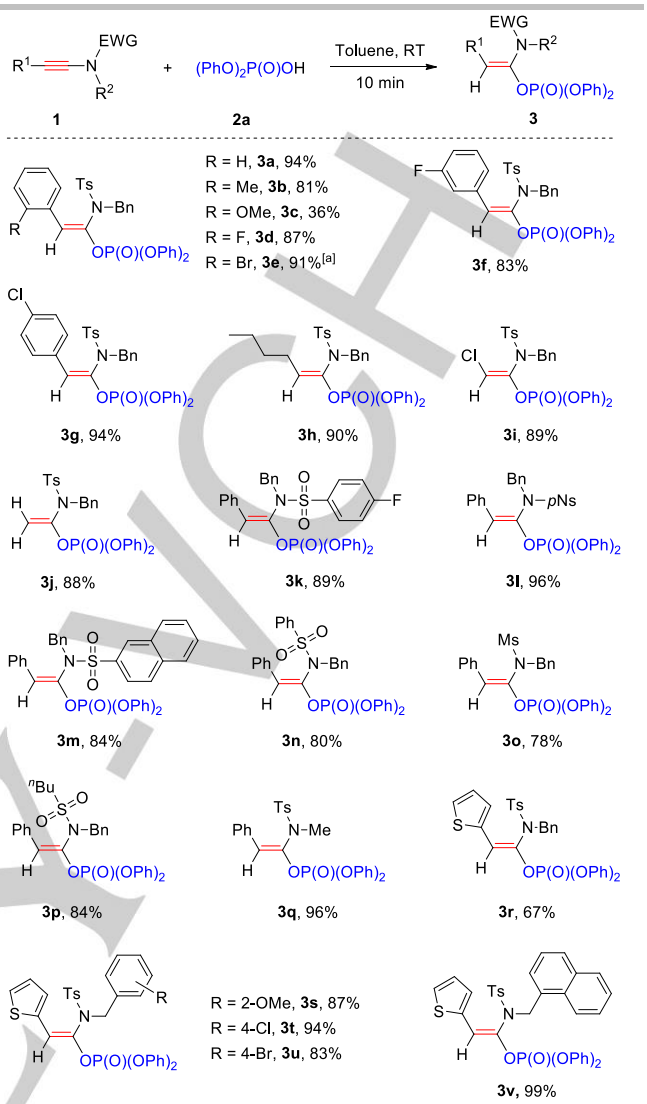


Figure 1. Solvent effects on the reaction. Conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), solvent (1.0 mL), RT for 10 min. Yield of **3a** was determined by HPLC using naphthalene as the internal standard.

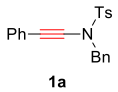
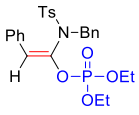
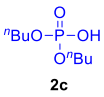
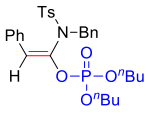
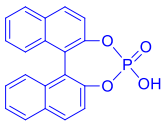
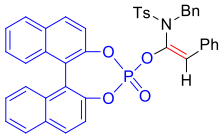
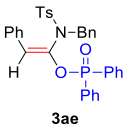
With the optimized conditions in hand, we then examined the scope with respect to ynamides (Scheme 3). The hydrophosphoryloxylation of model substrate **1a** led to the expected enol phosphate **3a** in 94% isolated yield. The *ortho*-Me group at phenyl ring of R^1 was well tolerated (**3b**), whereas varying to strong electron-donating group -OMe led to a decreased yield due to the facile formation of side hydrolyzed product (**3c**). The electron-withdrawing halides -F and -Br were compatible with the process as well, leading to the corresponding products **3d** and **3e** in 87% and 91% yield, respectively. The *meta*-F and *para*-Cl substituted aryl ynamides could be transformed into the desired enol phosphates in high yields (**3f**, **3g**). Submitting butyl-derived ynamide to the standard conditions delivered **3h** in 90% yield. Gratifyingly, chloro-substituted ynamide also worked well and product **3i** was afforded in 89% yield. Terminal ynamide proved to be a suitable substrate as well (**3j**). A range of sulfonyl groups on the nitrogen atom were further tested. The substituents on the phenylsulfonyl group exerted negeligible effect on the reaction outcome (**3k**, **3l**, **3n**). The reaction of bulky 2-naphthylsulfonyl derived ynamide also took place efficiently (**3m**). Furthermore, *N*-alkylsulfonyl ynamides could participate in this transformation, providing the corresponding products in good yields (**3o**, **3p**). *N*-Me substrate underwent hydrophosphoryloxylation smoothly to furnish adduct **3q** in 96% yield. Notably, 2-thienyl derived ynamides bearing different substituents on the benzyl group were also amenable to the protocol, resulting in the formation of the target products in 67–94% yields (**3r**–**3u**). When large 1-naphthylmethyl was attached to the nitrogen atom, the reaction also proceeded well to generate adduct **3v** in an excellent yield.



Scheme 3. Substrate scope with respect to ynamides. Conditions: **1** (0.15 mmol), **2a** (0.165 mmol), toluene (1.5 mL), RT for 10 min. Isolated yields are reported. [a]1 h.

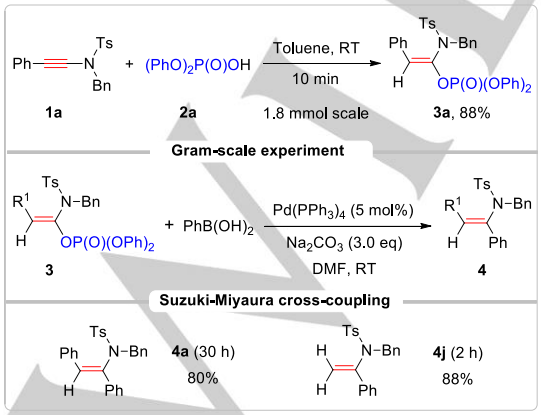
Subsequently, a range of phosphoric acids were scrutinized for the hydrophosphoryloxylation of ynamide **1a** (Table 1). It is found that an elevated temperature was required to promote the conversion of dialkyl phosphates. For example, diethyl phosphate **2b** could particpate in the transformation readily at 80 °C, affording adduct **3ab** in 76% yield. In the case of dibutyl phosphate **2c**, 81% yield of enol phosphate **3ac** was achieved under the optimized conditions. Pleasingly, the protocol could be successfully extended to BINOL-derived phosphoric acid **2d**, resulting in the formation of **3ad** in 98% yield. Furthermore, a treatment of diphenylphosphinic acid **2e** with ynamide **1a** in toluene also generated the desired product **3ae** in a good yield.[19]

Table 1. Addition of other phosphoric acids with ynamide.

Ynamide	Phosphoric acid	Enol phosphate	Yield (%)
 1a	 2b	 3ab	76[a]
	 2c	 3ac	81[a]
	 2d	 3ad	98[b]
	 2e	 3ae	78[b]

Conditions: [a]**1a** (0.15 mmol), **2** (0.165 mmol), toluene (1.5 mL), 80 °C for 4 h. [b]**1a** (0.165 mmol), **2** (0.15 mmol), toluene (1.5 mL), RT for 24 h. Isolated yields are reported.

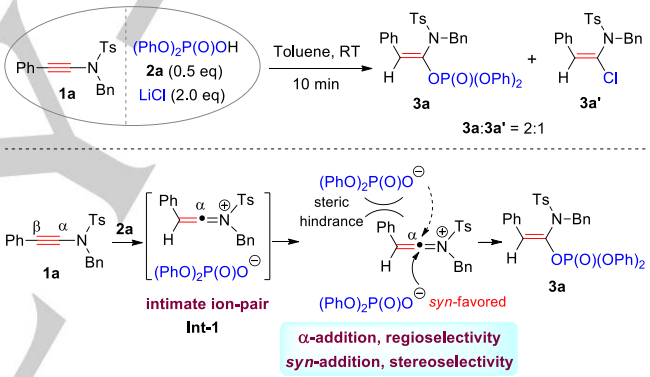
To illustrate the practicality of this approach, a gram-scale reaction was carried out (Scheme 4). When the addition of ynamide **1a** and diphenyl phosphate **2a** was amplified to 1.8 mmol, this transformation could also be completed within 10 min to give enol phosphate **3a** in 88% yield (1.0 g). Besides, the synthetic transformation of the resulting product was further investigated (Scheme 4). We were glad to find that enol phosphate **3a** and phenylboronic acid could undergo Suzuki-Miyaura cross-coupling at room temperature, delivering the expected product **4a** in 80% yield. Moreover, when terminal enol phosphate **3j** was employed as the partner, the coupling also proceeded in high efficiency (**4j**, 88%) and the reaction time could be shortened to 2 h.



Scheme 4. Gram-scale reaction and synthetic transformation.

To gain deeper insight into the reaction mechanism, a competitive experiment was conducted (Scheme 5). We envisioned that if a smaller nucleophile such as chloride anion was involved in the process, the addition between chloride anion and keteniminium ion should take place predomintantly. However, surprisingly, when a mixture of ynamide **1a**, diphenyl phosphate **2a** (0.5 eq) and LiCl (2.0 eq) in toluene was stirred at room temperature for 10 min, both adducts enol phosphate **3a** and vinyl chloride **3a'** were isolated with 2:1 molar ratio. This result suggests that the nucleophilic attack of phosphate anion preferably proceeds through an intimate ion-pair pathway.

Based on this experimental observation and the precedents on the hydrofunctionalizations of ynamide,[12,13] a plausible mechanism is depicted in Scheme 5. Ynamide **1a** is first protonated by phosphoric acid **2a** to furnish contact keteniminium/phosphate ion-pair **Int-1**. In this step, owing to the partial charge transfer from the lone pair on the nitrogen atom into carbon-carbon triple bond, the electron density of C_β in ynamide is significantly higher than that of C_α, so C_β should be protonated preferentially (**Int-1**). This selective protonation then leads to the following exclusive α-addition regioselectivity. The upper face of keteniminium intermediate **Int-1** is sterically hindered by the phenyl group. Thus, the nucleophile phosphate anion favors *syn* attack from the H side to C_α of **Int-1**, resulting in the formation of α-adduct **3a** with exclusive (*E*)-stereoselectivity.



Scheme 5. Competitive experiment and proposed mechanism.

In summary, we have described a metal-free hydrophosphoryloxylation of ynamides with phosphoric acids. This strategy enables a facile formation of useful enol phosphates with exclusive regio- and stereoselectivity. Other salient advantages include short reaction time, high yields, mild conditions, broad substrate scope, and good synthetic utility. This protocol will not only enrich the hydrofunctionalization of ynamides but also provide some guidance into designing new cross couplings for the synthesis of multi-substituted alkenes.

Acknowledgements

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Keywords: metal-free • phosphoric acids • ynamides • regioselectivity • enol phosphates

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[19] We also conducted the reaction of ynamide with hypophosphorous acid (H_3PO_2). However, because commercially available H_3PO_2 is an aqueous solution, only the adduct of ynamide with water was afforded (compound **3af** in page S10).

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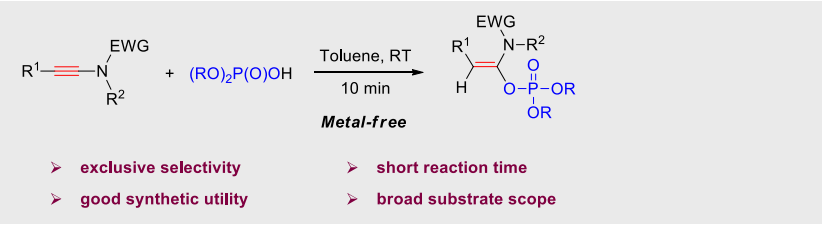

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Metal-Free Hydrophosphoryloxylation of Ynamides: Rapid Access to Enol Phosphates

An addition between phosphoric acids and ynamides is developed for the synthesis of amino-derived enol phosphates. The protocol features metal-free conditions, exclusive selectivity, short reaction time and easy scale-up. Notably, the resulting products could easily undergo Suzuki-Miyaura cross-coupling at room temperature.