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Regio- and Stereoselective Hydrophosphorylation of Ynamides: A Facile Approach to (*Z*)-*β*-Phosphor-Enamides

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Abstract: The first *trans*-selective *β*-hydrophosphorylation of ynamides, which provides a facile approach to (*Z*)-*β*-phosphor-enamide derivatives in moderate to excellent yields and with excellent regio- and stereoselectivity, is described. This transition-metal free reaction is featured with operationally simple procedure, mild reaction conditions, readily available starting materials, broad substrate scope and good functional-group tolerance. It is noted that the (*Z*)-*β*-phosphor-enamides can be prepared from the oxidation of the corresponding phosphine derivatives or the direct *β*-hydrophosphorylation of ynamides with diphenylphosphine oxide. In addition, *cis*-*trans* isomerization of (*Z*)-*β*-phosphor (V)-enamides can be easily realized to furnish the corresponding (*E*)-*β*-phosphor (V)-enamides. This advantageous feature enables the preparation of (*Z*)-*β*-phosphor (V)-enamides as well as (*E*)-*β*-phosphor (V)-enamides from the same starting materials.

Keywords: *β*-hydrophosphorylation; ynamides; *trans*-selective; (*Z*)-*β*-phosphor-enamides; transition-metal free

Ynamides have found widespread application as versatile building blocks in organic chemistry because of the appropriate balance between their stability and reactivity.[1] Consequently, functionalization of ynamides has received increasing attention over the past decades.[2] Theoretically, a ynamide has two polar resonance structures (Fig. 1).[3] The inherent polarization of the ynamide triple bond attributed to the electron-donating ability of nitrogen affords a keteniminium form, which undergoes regioselective addition to the *α*-carbon of activated and polarized alkynes (Fig. 1, eq 1).[4] While the extensive studies have been carried out on *α*-additions, "umpolung-type" *β*-additions, which originate from another polar resonance structure, i.e., the yniminium form, have been far less explored (Fig. 1, eq 2).[5] Because of the intrinsic difference in the reaction mechanism, *β*-addition of ynamides afford functionalized enamides with a complete switch in regioselectivity. Marek's pioneering work on the carbocupration of ynamides demonstrated that the

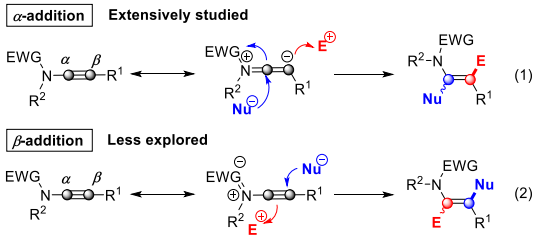

Figure 1. Functionalization of ynamides via *α*-addition or *β*-addition

regioselectivity of the nucleophilic addition reaction (*α*-addition) could be reversed to *β*-addition by exploiting the chelation effect between the transition metal catalyst and the electron-withdrawing group of the ynamide.[6] Using this concept, the transition metal catalyzed carbometallation of ynamides has been elaborated for the preparation of novel functionalized enamides.[7] In all these reactions, the aforementioned metal-containing intermediates were trapped by various electrophiles to afford multi-substituted enamides via *cis*-addition. In contrast, *trans*-selective *β*-addition of ynamides are rare,[8] apart from the addition of thiyl[9] and silyl radicals[10] to the *β*-position of ynamides. Therefore, the *trans*-

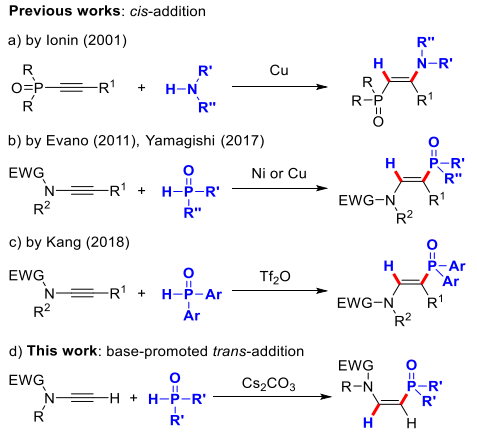

Figure 2. The preparation of *β*-phosphor-enamides

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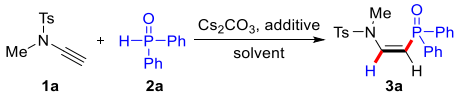
selective *β*-addition of ynamides is highly desirable to access unknown enamides, which are otherwise inaccessible via conventional chemistry.

1,2-N,P structural motifs are widely found in biologically important compounds[11] and frequently used ligands.[12] Despite the important applications of 1,2-N,P compounds in drug discovery and organometallic chemistry, only a few methods are available for their synthesis, especially *β*-phosphor-enamides.[13] Recently, *β*-addition of functionalized alkynes has emerged as an attractive alternative for the rapid preparation of *β*-phosphor-enamides. Ionin revealed that *β*-addition of amides to alkynylphosphonates in the presence of a copper catalyst affords *β*-phosphor-enamides (Fig. 2, eq a).[14] Evano reported the nickel-catalyzed hydrophosphorylation of internal ynamides with dialkyl phosphites to furnish *β*-phosphor-enamides with excellent regio- and stereoselectivity (Fig. 2, eq b).[15] In addition, Yamagishi and co-workers realized the regio- and stereoselective hydrophosphorylation of terminal ynamides by employing a copper catalyst (Fig. 2, eq b).[16] Very recently, Kang group developed a metal-free hydrophosphorylation of ynamides with diaryl phosphine oxides for the synthesis of *β*-phosphor-enamides (Fig. 2, eq c).[17] It is noted that only (*E*)-*β*-phosphor-enamides were obtained with *cis*-addition of the electrophiles in all these cases. A general method for the synthesis of (*Z*)-*β*-phosphor-enamides, which can serve as very useful building blocks and ligands, remains unexplored.[18] Considering the potential applications of (*Z*)-*β*-phosphor-enamides, efficient strategies for their synthesis are in great demand. Herein we report an unprecedented base-promoted hydrophosphorylation of ynamides to furnish diverse unknown (*Z*)-*β*-phosphor-enamides via the *trans*-selective *β*-addition of ynamides (Fig. 2, eq d).[19]

Table 1. Optimization of reaction conditions[a]



1a 2a 3a

entry	solvent	additive (equiv.)	time	yield (%)[b]
1	MeCN		24 h	65
2[c]	MeCN		24 h	54
3	CH_3NO_2		15 h	trace
4	DMSO		10 h	31
5	THF		20 h	trace
6	MeCN	TBAI (3.0)	10 h	59
7	MeCN	TBAB (3.0)	4 h	67
8	MeCN	TBAF (3.0)	4 h	70
9[d]	MeCN	TBAF (3.0)	4 h	--
10	MeCN	TBAF (1.0)	7 h	74
11	MeCN	TBAF (0.5)	7 h	77
12	MeCN	TBAF (0.2)	7 h	83

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Cs_2CO_3 (3.0 equiv) and additive in solvent (1.0 mL) at rt. [b]Isolated yields. *Z*:*E* > 99:1 (determined by crude ^{1}H NMR). [c]1.5 equiv of Cs_2CO_3 was used. [d]Without Cs_2CO_3.

Dodd and co-workers reported that *trans*-selective *β*-addition of indoles to ynamides is an efficient strategy to furnish functionalized indoles.[20] Very recently, our group discovered that the base-promoted hydroamidation of ynamides is a general synthetic strategy for (*Z*)-ethene-1,2-diamides with excellent regio- and stereoselectivity.[21] Thus inspired, we envisioned that the synthesis of (*Z*)-*β*-phosphor-enamides would be possible if the base-promoted hydrophosphorylation of ynamides could be realized. In the initial studies, we chose the addition of diphenylphosphine oxide **2a** to *N*-methylynetoluenesulfonamide (MYTsA **1a**) as a model reaction. To our delight, the hydrophosphorylation product (*Z*)-*β*-phosphor-enamide **3a** was isolated in 65% yield when the reaction was performed in MeCN at room temperature with Cs_2CO_3 as the base (Table 1, entry 1). The structure of **3a** was confirmed by X-ray crystallography and NMR analysis (for details, see the Supporting Information).[22] Screening of the solvents revealed that MeCN was the best choice for this transformation (Table 1, entries 3−5). Further optimization showed that additives are beneficial for improving the reaction efficiency and shortening the reaction time (Table 1, entries 6−8). However, no hydrophosphorylation product could be detected when 3 equiv of TBAF was used alone (Table 1, entry 9). The best results were obtained when 0.2 equiv of tetrabutylammonium fluoride (TBAF) was used as the additive (Table 1, entries 10−12).

With the optimized reaction conditions in hand, we next investigated the substrate scope of the addition reaction between ynamides and diphenylphosphine oxide **2a** (Scheme 1, reaction conditions A). As shown in Scheme 1, all the reactions proceeded to afford the products in good to excellent yields with excellent regio- and stereoselectivity. Ynamides bearing alkyl groups and functionalized alkyl groups on the nitrogen atom were converted to the corresponding products (**3a**−**h**) in 83−99% yields. Substitutions on the aryl ring of the ynamides were well tolerated under the reaction conditions (**3i**−**l**). Treatment of *N*-ethynyl-*N*-methylmethanesulfonamide **1m** furnished the desired product **3m** in 91% yield. Interestingly, hydrophosphorylation of ynecarbomate **1n** afforded the target product **3n** in acceptable yield. However, there is no reaction at all when ynamides bearing bulky aryl or cyclohexyl group on the nitrogen atom is employed as the substrate.

To further broaden the scope of this transformation, we employed various dialkyl phosphonate as the substrates. By slight modification of the reaction conditions (Scheme 1, reaction conditions **B**, see the Supporting Information for details), the target (*Z*)-*β*-phosphor-enamides (**3o**−**t**) could be efficiently synthesized via *β*-addition of diethyl phosphonates to a series of ynamides. The dialkyl phosphonates reacted smoothly in this reaction system to provide the corresponding addition products (**3u**−**x**) in moderate to good yields.

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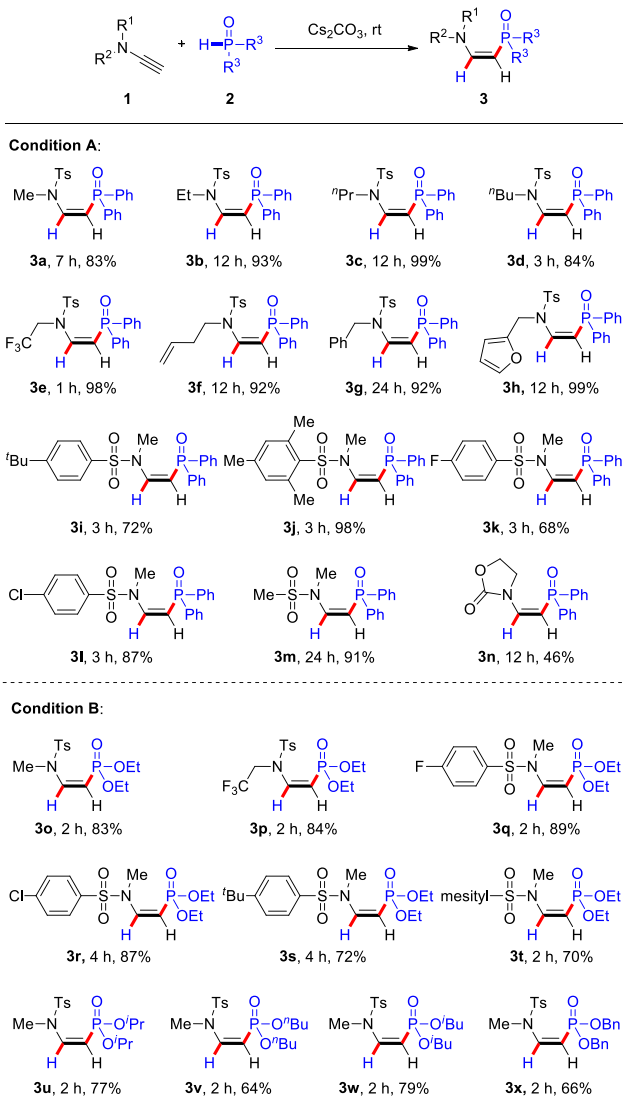
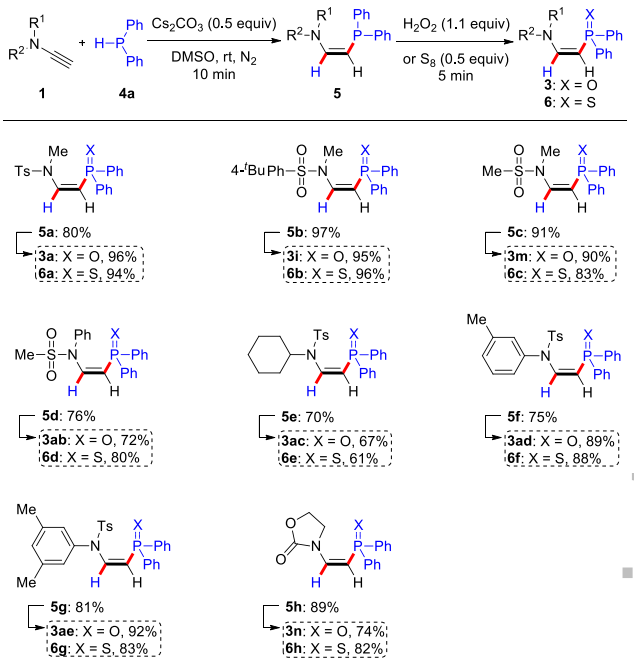


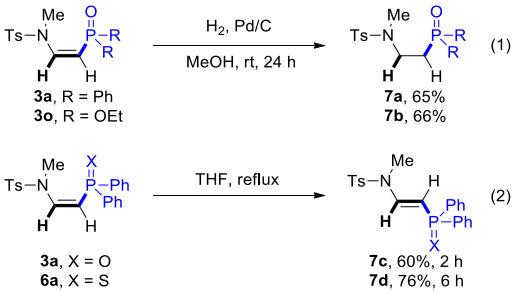
Scheme 1. Hydrophosphorylation of Ynamides with $HP(O)R_2$. Reaction conditions **A**: **1** (0.2 mmol), diphenylphosphine oxide **2** (0.6 mmol), Cs_2CO_3 (0.6 mmol) and TBAF (0.2 equiv) in MeCN (1.0 mL) at rt. *Z*:*E* > 99:1 (determined by crude ^{1}H NMR). Reaction conditions **B**: **1** (0.4 mmol), dialkyl phosphonate **2** (0.2 mmol) and Cs_2CO_3 (0.4 mmol) in DMSO (1.0 mL) at rt. *Z*:*E* > 99:1 (determined by crude ^{1}H NMR).

Following the successful hydrophosphorylation of ynamides, we became interested in extending this strategy to trivalent P-H compound diphenylphosphine **4a**, which would provide (*Z*)-2-(diphenylphosphino)-ethenamide derivatives. Under the optimized reaction conditions (See the Supporting Information for details), the hydrophosphorylation of ynamides proceeded smoothly to give the corresponding *β*-addition products (**5a**–**h**) in 70–97% yields with excellent regio- and stereo-selectivity (Scheme 2). Notably, slight oxidation of the phosphine product to phosphine oxide was observed during the reaction and processing. Thus, an inert reaction atmosphere was employed to ensure the isolation of (*Z*)-2-(diphenylphosphino)-ethenamides **5** in good yields. On the contrary, further treatment of



Scheme 2. Hydrophosphorylation of Ynamides with Diphenylphosphine. Reaction conditions: **1** (0.2 mmol), **4a** (0.24 mmol) and Cs_2CO_3 (0.1 mmol) in DMSO (1.0 mL) at rt for 10 min under N_2 to afford products **5**, and then H_2O_2 (1.1 equiv) or S_8 (0.5 equiv) was added for 5 min afford products **3** or **6**. *Z*:*E* > 99:1 (determined by crude ^{1}H NMR).

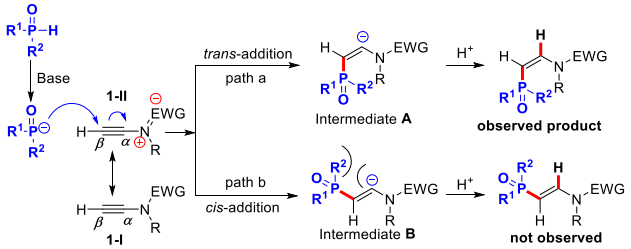
the addition products **5** with H_2O_2 or S_8 in a one-pot manner offered the corresponding oxidized products **3** or sulfidized products **6** in excellent yields. The structure of **6b** was confirmed by X-ray crystallography (for details, see the Supporting Information).[22] It is noteworthy that (*Z*)-2-(diphenylphosphoryl)vinylamides (**3ab**–**ae**), which cannot be accessed via the addition of diphenylphosphine oxide to ynamides, can be prepared efficiently by using this two-step, one-pot strategy.



Scheme 3. Reduction and Z/E-isomerization of (Z)-hydrophosphoryl-enamides.

The synthetic application of these addition products was then explored. Hydrogenation of addition products **3a** and **3o** in the presence of Pd/C with a H_2 balloon provided the reduced products **7a** and **7b** in 65% and 66% yields, respectively (Scheme 3, eq 1). Interestingly, (*Z*)-*β*-phosphor-enamides **3a**

and **6a** could be converted into the respective (*E*)-*β*-phosphor-enamides **7c** and **7d** in 60% and 76% yield by refluxing in THF (Scheme 3, eq 2). Such transformation provides an additional advantage for obtaining both (*Z*)- and (*E*)-*β*-phosphor-enamides from the same starting materials, and is expected to be remarkably useful in organic synthesis. Both (*Z*)- and (*E*)-configuration of these enamides were confirmed by the $^{3}J_{H\text{-}H}$ coupling constant of the vicinal two alkenyl protons and the X-ray analysis of **7c** (for details, see the Supporting Information).[22]



Scheme 4. Plausible Reaction Mechanism

With these results in hand, a plausible mechanism of this transformation was proposed in Scheme 4. Deprotonation of nucleophiles, including $(Ph)_2P(O)H$, $(RO)_2P(O)H$, and $(Ph)_2PH$, by Cs_2CO_3 would provide the anion Nu^-. And then, *β*-addition of Nu^- to the resonance structure of ynamides (**1-II**) generateed the anion intermediate **A** or **B** through *trans*- or *cis*-1,4-addition, respectively. The formation of *cis*-addition intermediate **B** is unfavorable due to the coulomb repulsion between the negative charge and phosphoryl functional group.[20] Finally, the protonation of *trans*-addition intermediate **A** afforded the corresponding (*Z*)-product with excellent regio- and stereoselectivities.[23]

In conclusion, we have developed the first synthetic strategy for functionalized (*Z*)-*β*-phosphor-enamides via an unprecedented base-promoted *trans*-selective *β*-hydrophosphorylation of ynamides, without using any transition-metal catalyst.[24] The reactions proceeded smoothly with exceptionally broad functional group tolerance under simple and mild conditions. Apart from pentavalent phosphine substrates, trivalent phosphine substrates also worked smoothly in this transformation to provide the corresponding trivalent phosphine products, which in turn could be converted into pentavalent phosphine products by subsequent oxidation or sulfidation treatment in a one-pot manner. Additionally, the (*Z*)-*β*-phosphor-enamides can be easily isomerized to (*E*)-*β*-phosphor-enamides. This feature offers another advantage in that both (Z)- and (*E*)-*β*-phosphor-enamides could be obtained from the same starting materials. This synthetic strategy would pave the way for further research on (*E*)-*β*-phosphor-enamides and for expanding their synthetic application.

Experimental Section

General procedure I: synthesis 3a-3n:

To an oven-dried Schlenk tube equipped with a magnetic stir bar was added ynamides (0.2 mmol), diphenylphosphine oxide (0.6 mmol), Cs_2CO_3 (0.6 mmol), TABF (0.04 mmol) and solvent MeCN (1.0 mL). The reaction mixture was stirred at room temperature and monitored by TLC. Upon the reaction completion, H_2O was added to quench the reaction and the mixture was extracted with ethyl acetate (1.0 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford the desired products **3a-3n**.

General procedure II: synthesis 3o-3x:

To an oven-dried Schlenk tube equipped with a magnetic stir bar was added dialkyl phosphate (0.2 mmol), ynamides (0.4 mmol), Cs_2CO_3 (0.4 mmol), and solvent DMSO (1.0 mL). The reaction mixture was stirred at room temperature and monitored by TLC. Upon the reaction completion, H_2O was added to quench the reaction and the mixture was extracted with ethyl acetate (1.0 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford the desired products **3o-3x**.

General procedure III: synthesis 5a-5h

To an oven-dried Schlenk tube equipped with a stir bar was added ynamide (**1**) (0.20 mmol,) and Cs_2CO_3 (0.10 mmol). After the addition of all solid reagents, the reaction vessel was evacuated and flushed with N_2. Then a solution of diphenylphosphine (**4a**) (0.24 mmol) in dry DMSO (1.0 mL) was added by syringe. The reaction mixture was stirred at room temperature for 10 min. Then H_2O was added to the system to quench the reaction, and the mixture was extracted with ethyl acetate (1.0 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by a silica gel column to afford the desired product **5a-5h**.

General procedure IV: synthesis 3a, 3i, 3m, 3n, 3ab-3ae, 6a-6h

To an oven-dried Schlenk tube equipped with a stir bar was added ynamide (**1**) (0.20 mmol,) and Cs_2CO_3 (0.10 mmol). After the addition of all solid reagents, the reaction vessel was evacuated and flushed with N_2. Then a solution of diphenylphosphine (**4a**) (0.24 mmol) in dry DMSO (1.0 mL) was added by syringe. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture oxidized with H_2O_2 (30% aq, 22 μL, 1.1 equiv) or S_8 (25.7 mg, 0.10 mmol, 0.5 equiv) for 5 min. Then H_2O was added to the system to quench the reaction, and the mixture was extracted with ethyl acetate (1.0 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by a silica gel column to afford the desired product **3a**, **3i**, **3m**, **3n**, **3ab-3ae, 6a-6h**.

Acknowledgements

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[22] CCDC 1840555 (**3a**), CCDC 1840553 (**6b**), and CCDC 1870931 (**7c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] The protonation process was confirmed by deuterated product firmed in the presence of D_2O (for details, see the supporting information).

[24] Our efforts to expand the chemistry to internal ynamides and to remove the protecting group of the (Z)-*β*-phosphor-enamides product were failed.

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