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Csp^3–P versus Csp^2–P Bond Formation: Catalyst-Controlled Highly Regioselective Tandem Reaction of Ene-Yne-Ketones with *H*-Phosphonates

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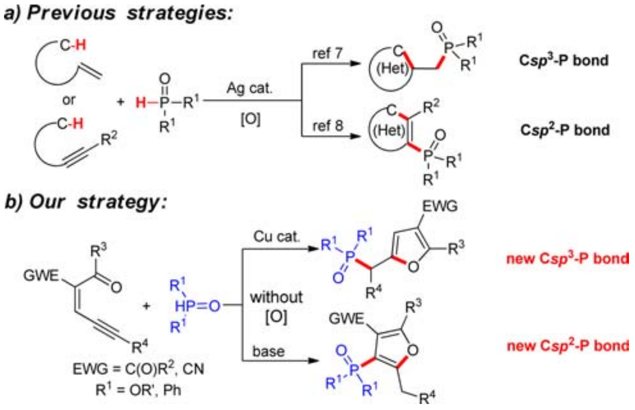
S *Supporting Information*

ABSTRACT: Under copper-catalyzed or base-promoted conditions, a wide range of ene-yne-ketones react with *H*-phosphonates to afford various phosphorylated furans in good yields. A copper carbene generation or a Michael addition is proposed as the key step in the selective construction of the Csp^3–P or Csp^2–P bond, which is supported by carbene capture reactions and interval ^{31}P NMR experiments. Furthermore, this method features inexpensive metal catalysts, no usage of oxidant, and high atom economy, which make it attractive and practical.

Phosphorylated heterocycles and derivatives represent an important class of molecules that are closely related to life science.[1] Recent studies have revealed that heterocycles containing P-substituents show unique bioactivities and chemical properties,[2] which lead them to broad applications in organic synthesis,[3] medicinal chemistry,[4] and materials chemistry.[5] In light of this, the development of more efficient and concise synthetic methods for C–P bond construction on heterocycles is highly desirable.[6] In the past years, tremendous efforts have been made toward the synthesis of phosphorylated heterocycles through C–P bond construction from simple materials like alkenes or alkynes. Several extensively valuable methods have been established and developed. For example, Ag-catalyzed radical cascade reactions have provided useful approaches to synthesize phosphorylated oxindoles, coumarins, aza-decenones, and so on. These reactions were initiated by the addition of P-centered radicals to unsaturated alkenes or alkynes, constructing the corresponding Csp^3–P or Csp^2–P bond.[7,8] However, an extra oxidant was needed in most of these methods, and the substituted alkenes or alkynes, which have been reported to afford the corresponding phosphorylated heterocycles, were still very limited (Scheme 1a).

Furan derivatives are important frameworks of many biologically active molecules and drug intermediates.[9] However, synthetic methods of phosphorylated furans from alkenes or alkynes have been less explored until now.[10] Previously, our group contributed to the study of the synthesis of highly functionalized furans using alkynes as a building block.[11] Among these substituted alkynes, conjugated ene-yne-ketone[12] is supposed to be an active and innovative substrate because it is not only a carbene precursor under transition-metal-catalyzed conditions but also a Michael addition acceptor due to the α,β-unsaturated ketone moiety. We herein report an efficient and highly regioselective strategy for the synthesis of various phosphorylated furans via Cu-catalyzed Csp^3–P or base-promoted Csp^2–P bond construction between ene-yne-ketones and *H*-phosphonates.[13] To the best of our knowledge, the selective construction of different C–P bonds to afford P-containing heterocycles from the same starting materials by a catalyst selection has not been reported before (Scheme 1b).

Scheme 1. Synthesis of P-Containing Heterocycles from Alkenes or Alkynes through C–P Bond Formation



At the outset of our studies, we treated ene-yne-ketone **1a** with diethyl phosphite (**2a**) as the model substrates for reaction development (Table 1). Initially, **3aa** was obtained in 71% yield under simple conditions, where CuBr was used as the catalyst in Et_2O at 80 °C for 2 h (entry 1). The organic base DIPEA was found to increase the yield to 89% (entry 2). Notably, when Cs_2CO_3 was added as a base, **4aa** was detected while the yield of

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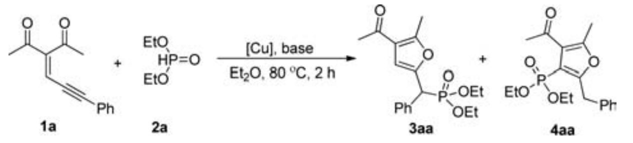
Table 1. Optimization of the Reaction Conditions[a]



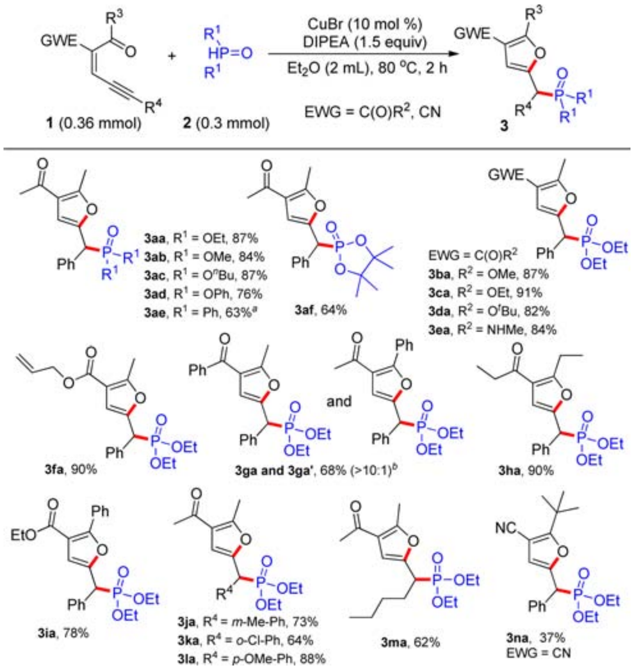
entry	[Cu]	base	yield of **3aa**[b] (%)	yield of **4aa**[b] (%)
1	CuBr		71	nd
2	**CuBr**	**DIPEA**[c]	**89 (87)**	**nd**
3	CuBr	Cs_2CO_3	trace	58
4	CuBr	K_2CO_3	39	19
5	CuBr	DABCO	trace	48
6	CuBr	*t*-BuOLi	12	32
7		Cs_2CO_3	nd	62
8[e]		**Cs_2CO_3**[d]	**nd**	**92 (89)**

[a]Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), [Cu] (10 mol %), base (1.5 equiv), and 1.0 mL of Et_2O at 80 °C for 2 h unless otherwise noted. [b]Yields were analyzed by GC-MS using *n*-dodecane as an internal standard. [c]*N*,*N*-Diisopropylethylamine. [d]0.5 equiv. [e]100 °C for 1 h in DMF.

3aa dropped dramatically (entry 3). Similar results were also obtained when K_2CO_3, DABCO, or *t*-BuOLi was used (entries 4–6). We suspected that a certain strong base might change the reaction pathway in this catalytic system, and the copper salts should not play a role in the formation of **4aa** (see Supporting Information for details). As expected, a single product of **4aa** was gained in 62% yield with only Cs_2CO_3 as the base and without CuBr as the catalyst (entry 7). Further investigation indicated that adding 0.5 equiv of Cs_2CO_3 and heating at 100 °C for 1 h in DMF led to the highest yield of **4aa** (entry 8).

With the optimized reaction conditions in hand (Table 1, entry 2), we first evaluated the scope for the formation of (furan-2-ylmethyl)phosphonates (Scheme 2). In regard to the *H*-phosphonates, dialkyl *H*-phosphonates (**2a–2c** and **2f**) and diphenyl *H*-phosphonates (**2d**) all could be used as the substrates, generating the corresponding alkylphosphonates (**3aa–3ad** and **3af**) in 64–87% yields. It is worth noting that diphenylphosphine oxide can also be applied to the preparation of alkyldiphenylphosphine oxide in 63% yield by using Cs_2CO_3 as the base, which should be a good supplement to the Csp^3–P bond formation methods. The scope of this transformation was next explored by using various ene-yne-ketones **1b–1m** and **2a**. The influence of the R^2 and R^3 groups, which are adjacent to the carbonyl moiety, were studied. This novel transformation showed high functional group tolerance (such as R^2 = OMe, O^{t}Bu, NHMe, OCH_2CHCH_2; R^2 = R^3 = Et; R^2 = OEt, R^3 = Ph), and in most cases, the corresponding products (**3ba–3fa**, **3ha–3ia**) were obtained in good yields. Notably, the mixture of (*E*)- and (*Z*)-ene-yne-ketones afforded the single products, and only the ketone carbonyl oxygen acted as a nucleophile in the cyclization.[12c] Thus, to examine the regioselectivity, we synthesized **1g** for this transformation. Intriguingly, the desired products **3ga** and **3ga′** were obtained in 68% yield with a regioselectivity of more than 10:1. We supposed that steric hindrance acted as an important factor in this case. Moreover, the reaction was found to tolerate a broad range of R^4 groups on the alkyne terminus, including substituted arenes and alkanes (**3ja–3ma**). Intriguingly, 5-phenyl-2-pivaloylpent-2-en-4-ynenitrile (**1n**) could be also converted into **3na** in 37% yield by Cu catalysis.

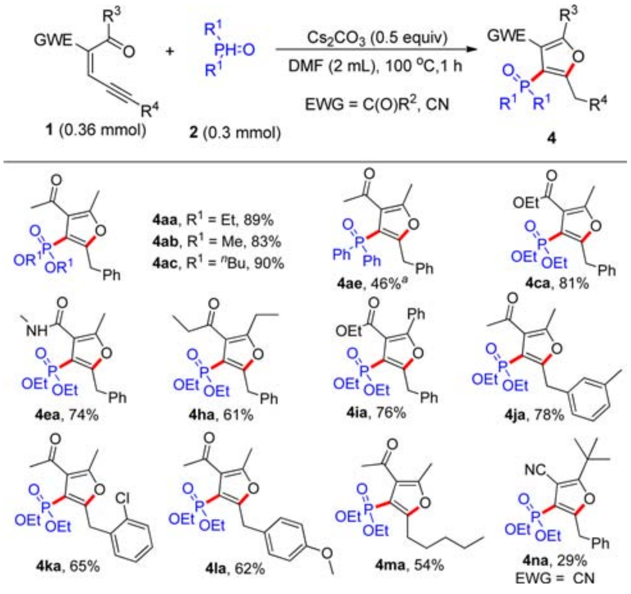
Scheme 2. Substrate Scope for the Formation of (Furan-2-ylmethyl)phosphonates



[a]Cs_2CO_3 as the base, **4aa** was also isolated with a yield of 27%. [b]Detected by GC/MS using *n*-dodecane as an internal standard.

We next examined the scope of the synthesis of **4** through Cs_2CO_3-promoted phosphonation and annulation. As shown in Scheme 3, a series of *H*-phosphonates afforded the corresponding phosphorylated furans in good yields (**4aa–4ac**). Diphenylphosphine oxide was also a suitable substrate for this cyclization, by adding 1.5 equiv of Cs_2CO_3 and heating for 12 h, and the target product **4ae** was isolated in 46% yield. We then investigated the scope of R^2 and R^3 groups. For R^2 = OEt,

Scheme 3. Substrate Scope for the Formation of Furan-3-ylphosphonates



[a]1.5 equiv of Cs_2CO_3 was used for 12 h.

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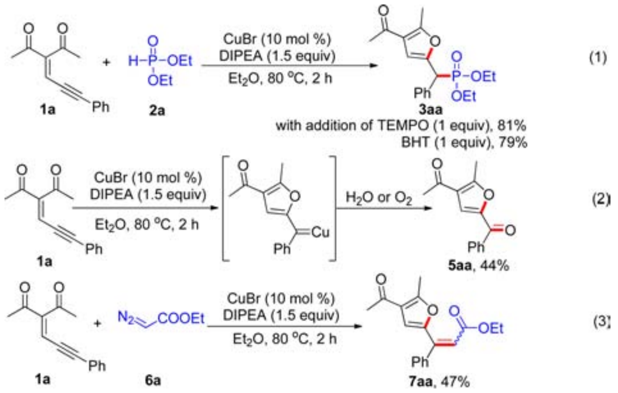
NHMe, $R^2 = R^3 =$ Et, or $R^2 =$ OEt, $R^3 =$ Ph, the ene-yne-ketones afforded the corresponding products in good yields (**4ca**, **4ea**, **4ha**, **4ia**). Similarly, only the ketone carbonyl oxygen acted as nucleophile in this process. Furthermore, substituted aryl alkynes and alkyl alkynes participated in this transformation, as well, thus leading to the furans **4ja**−**4ma** in moderate yields. When **1n** and **2a** were used in the Cs_2CO_3-promoted reaction system, the transformation afforded diethyl (2-benzyl-4-cyano-5-methylfuran-3-yl)phosphonate (**4na**), albeit with lower efficiency.

To gain more insight into the Cu-catalyzed alkyl phosphonation reaction, we first conducted radical capture reactions by adding a radical-trapping reagent (TEMPO) or a radical inhibitor (BHT) to the reaction system. Under the above two conditions, the formation of **3aa** was unaffected on the whole. These observations indicated that there should not be a radical pathway in this reaction (Scheme 4, eq 1). To confirm whether a copper carbene intermediate existed, we performed the reaction in the absence of **2a** to give the (2-furyl)carbene complex, which further underwent oxidation or hydrolysis to generate **5aa** in 44% yield. What's more, when ethyl diazoacetate (**6a**) was used to replace **2a** under the standard conditions, vinyl furan **7aa** was obtained in 47% yield. On the basis of these studies and several previous reports,[12a,14] we deduced that a copper carbene complex was possibly formed during this cascade process (Scheme 4, eqs 2 and 3).

Scheme 4. Mechanistic Studies



On the other hand, to analyze the reaction process for the synthesis of **4aa**, we tried to trap the intermediates but failed since the transformation was a rapid process. Thus, the reaction was traced by ^{31}P NMR spectroscopy, as shown in Figure 1. In a nuclear magnetic tube, a mixture of ene-yne-ketone **1a**, *H*-phosphonate **2a**, and Cs_2CO_3 was added into a solvent of *N*,*N*-dimethylformamide-d_7. The sample was immediately tested for a ^{31}P NMR spectrum. The first spectrum showed a single signal at 7.31 ppm, which was assigned as the starting material **2a**. After being heated at 100 °C for 5 min, the expected phosphorylated product **4aa** was produced (single peaks at 13.03 ppm), while four other new peaks at 12.73, 12.42, 12.23, and 12.12 ppm appeared at the same time. As time passed, the ^{31}P NMR signals of **2a** disappeared gradually and the signals of **4aa** increased. Importantly, the four uncertain peaks faded away as well in 50 min. Thus, we inferred that the signals might belong to the reaction intermediates $\mathbf{A_2}$, $\mathbf{B_2}$, $\mathbf{C_2}$, and $\mathbf{D_2}$ (see the proposed catalytic cycle in the Supporting Information). However, we could not determine the four signals in these stacked spectra. The reaction was completely finished after 1 h according to the spectra (Figure 1).

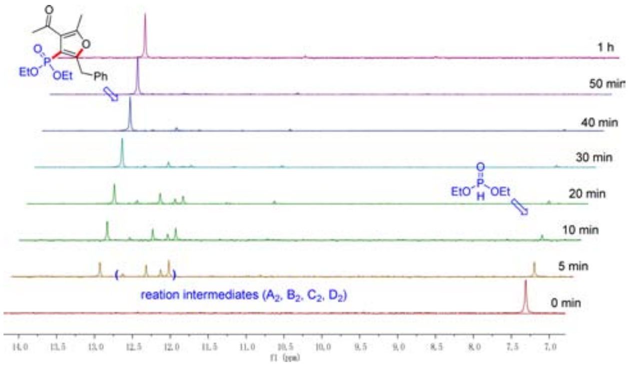


Figure 1. ^{31}P NMR stacked spectra for the formation of **4aa**.

Taking the experimental results into account, we proposed the mechanisms for the synthesis of **3** or **4** (see the proposed catalytic cycle in the Supporting Information). For reaction (i), the alkyne moiety of ene-yne-ketone **1a** was activated by the copper species at first, which was then attacked by the carbonyl oxygen through 5-*exo-dig* cyclization, leading to copper carbene species $\mathbf{A_1}$. In the presence of phosphinous acid **2a**′, the tautomeric form of *H*-phosphonate **2a**, carbene intermediate $\mathbf{A_1}$ was trapped to form the copper-associated ylide $\mathbf{B_1}$.[15] Then, a copper carbene migratory insertion process was followed to give intermediate $\mathbf{C_1}$. Finally, the phosphonation product **3aa** was obtained by catalyst dissociation and the Cu(I) species was regenerated. On the other hand, reaction (ii) began with the process of Michael addition between ene-yne-ketone **1a** and *H*-phosphonate **2a** using Cs_2CO_3 as the base, leading to intermediate $\mathbf{A_2}$ and allenyl intermediate $\mathbf{B_2}$.[16] Afterwards, a subsequent nucleophilic attack by the carbonyl oxygen atom generated intermediate $\mathbf{C_2}$. In the presence of Cs_2CO_3, a deprotonation occurred to produce the intermediate $\mathbf{D_2}$, followed by a protonation to give the final phosphorylated furan **4aa**.

In summary, we have developed a highly efficient protocol for the preparation of various phosphorylated furans via a Cu-catalyzed Csp^3−P or base-promoted Csp^2−P bond formation, involving 5-*exo-dig* cyclization, carbene migratory insertion, and Michael addition. Not only *H*-phosphonates but also diphenylphosphine oxides react with a wide range of ene-yne-ketones to afford the products in moderate to good yields under mild reaction conditions. Furthermore, no use of oxidant, high atom economy, and good regioselectivity of products via catalyst-controlled make this method a new valuable approach for the formation of precious C−P bonds. Mechanistic studies including radical or carbene capture reactions and interval ^{31}P NMR experiments have been conducted to clarify the reaction pathways. Further applications of this reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03415.

Experimental section, characterization of all compounds, and copies of ^1H and ^{13}C NMR spectra for selected compounds (PDF)

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Notes

The authors declare no competing financial interest.

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