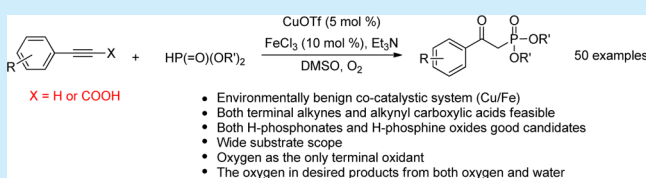


β -Ketophosphonate Formation via Aerobic Oxyphosphorylation of Alkynes or Alkynyl Carboxylic Acids with H-Phosphonates

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S Supporting Information

ABSTRACT: A synergistic Cu/Fe-catalyzed aerobic oxyphosphorylation of alkynes or alkynyl carboxylic acids with H-phosphonate is disclosed. The useful β -ketophosphonate products were obtained in good yields under oxygen atmosphere in a novel way. This reaction exhibits a wide substrate scope, and the mechanistic experiments indicate that a radical mechanism forms both C–P and C=O bonds simultaneously. This mechanism contrasts existing aerobic difunctionalization of alkynes.

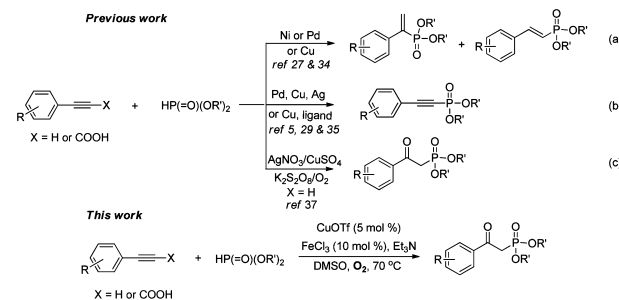


Because carbonyl-containing organic compounds play a tremendously important role in synthetic chemistry, efficient construction of carbonyl-containing compounds remains a long-standing goal in organic chemistry. Dioxygen is an ideal oxidant to access these compounds owing to its abundance, inexpensiveness, and environmentally benign feature.^{1,2} Terminal alkynes have also been extensively used in numerous transition-metal-catalyzed transformations during the past decade. In spite of their ubiquity in these processes, the C–C triple bond generally remains intact during aerobic transformations.^{3–7} For these reasons, creating C=O bonds from C–C triple bonds using dioxygen as both the oxidant and oxygen source has motivated organic chemists and becomes a promising field in modern synthetic chemistry. Despite these efforts, there are only a few examples reported to date.^{8–10}

The limited nature of these examples underscore that the development of efficient and practical methods that produce carbonyl compounds via difunctionalization of alkynes under dioxygen atmosphere remain an urgent and a tremendous challenge for modern synthetic chemistry.

β -Ketophosphonates are an extremely useful class of carbonyl- and phosphorus-containing organic compounds. In addition to possessing interesting bioactivities, they are key intermediates in the well-known Horner–Wadsworth–Emmons (HWE) reaction to construct α,β -unsaturated carbonyl compounds^{11–13} as well as versatile precursors for various synthetically useful transformations.^{14–18} Great efforts have been devoted to constructing β -ketophosphonate scaffolds, including the acylation of alkylphosphonates under basic conditions,^{19,20} the hydration of alkynylphosphonates,²¹ Arbuzov reaction,²² or the oxyphosphorylation of alkenes.²³ Because of the importance of phosphorus-containing compounds in organic synthesis, biology, and material sciences,^{24–26} developing transition-metal-catalyzed cross coupling between terminal alkynes and

Scheme 1. Transition-Metal-Catalyzed Reaction between Alkynes or Alkynyl Carboxylic Acids and H-Phosphonates



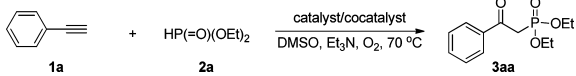
H-phosphonates has been pursued. Despite these advances, in most cases only alkenylphosphonates (Scheme 1a)²⁷ or alkynylphosphonates (Scheme 1b)⁵ can be formed. Using alkynyl carboxylic acids as a common practical surrogate for terminal alkynes has attracted significant attention recently and is widely used in transition-metal-catalyzed coupling reactions to generate new C–C, C–N, C–S, or C–P bonds.^{28–36} For the C–P bond formation, however, once again only alkenylphosphonates (Scheme 1a)³⁴ or alkynylphosphonates (Scheme 1b)^{29,35} were obtained. During the preparation and submission of this manuscript, Zhao and co-workers reported an elegant synthesis of β -ketophosphonates directly from alkynes and dialkyl H-phosphonates in the presence of AgNO₃/CuSO₄ and K₂S₂O₈ (Scheme 1c).³⁷ Herein, we disclose a Cu/Fe-co-catalyzed reaction that constructs β -ketophosphonates from alkynes or propiolate acids and H-phosphonates using O₂ as the

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terminal oxidant. Compared to Zhao's method, our reaction employs a more environmentally benign catalytic system (Fe/Cu) with simple operation and exhibits a wider substrate scope and both terminal alkynes and alkynyl carboxylic acids feasible under the standard conditions. Simultaneously, molecular oxygen itself serves as the only terminal oxidant and enables this transformation. Our mechanistic studies suggest that oxygen in the carbonyl group of β -ketophosphonate originates from both molecular oxygen and water, which is in contrast to precedent difunctionalization of alkynes.

To determine if the oxyphosphorylation of alkynes was feasible, we commenced our study with phenylacetylene (**1a**) and H-diethyl phosphonate (**2a**) as a model reaction (Table 1).

Table 1. Optimization of the Reaction Parameters^a

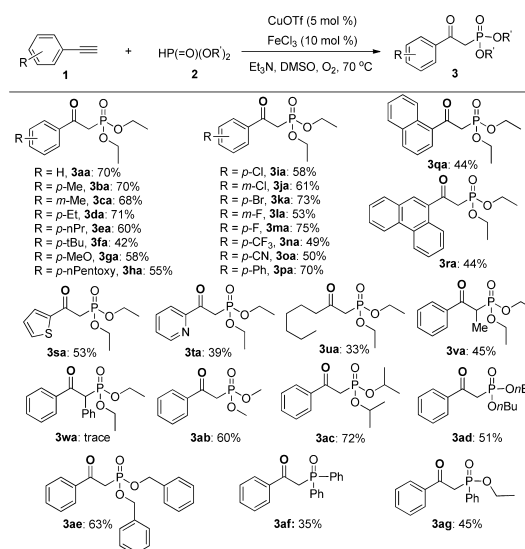


entry	catalyst	cocatalyst	temp (°C)	yield (%) ^b
1	CuOTf (10 mol %)	FeCl ₃ (5 mol %)	60	28
2	CuOTf (10 mol %)	FeCl ₂ (5 mol %)	60	9
3	CuOTf (10 mol %)	FeBr ₃ (5 mol %)	60	26
4	CuOTf (10 mol %)	-	60	N.D.
5	-	FeCl ₃ (5 mol %)	60	17
6	CuOTf (5 mol %)	FeCl ₃ (5 mol %)	60	33
7	CuOTf (5 mol %)	FeCl ₃ (10 mol %)	60	40
8	CuOTf (5 mol %)	FeCl₃ (10 mol %)	70	76 (70)^c
9	CuOTf (5 mol %)	FeCl ₃ (10 mol %)	80	55
10 ^d	Cu(OTf) ₂ (5 mol %)	FeCl ₃ (10 mol %)	70	10
11 ^e	Cu(OTf) ₂ (5 mol %)	FeCl ₃ (10 mol %)	70	-

^aReaction conditions: phenylacetylene **1a** (0.5 mmol), H-diethyl phosphonate **2a** (2.0 mmol), Cu catalyst and Fe co-catalyst in DMSO (0.5 M), Et₃N (0.5 mmol), O₂ (balloon), 24 h. ^bGC yield. ^cIsolated yield in parentheses. ^dThe reaction was conducted under air. ^eThe reaction was performed under N₂ atmosphere.

First, we examined if a metal-free oxidative process was possible by using only a base following the report by Lei and co-workers.⁹ Unfortunately, no desired products were ever isolated even after extensive screening (for details, see the Supporting Information (SI)). A series of transition-metal salts were then screened, and we were delighted to find that when 10 mol % of CuOTf was used together with 5 mol % of FeCl₃, the desired product β -ketophosphonate was formed in 28% isolated yield (Table 1, entry 1). Among the other iron salts screened, we found that only FeBr₃ and FeCl₃ produced product. Changing the oxidation state or the counterion of the iron salt resulted in only trace amounts of the β -ketophosphonate (Table 1, entries 1–3, and Table S2, SI). Solvent and base screenings (Table S3, SI) indicated that DMSO and triethylamine are the best choices, while other solvents and bases were all less effective in this transformation. Catalyst and co-catalyst loading screenings suggested that 5 mol % of CuOTf and 10 mol % of FeCl₃ gave the best yield of desired product (Table 1, entry 8). When temperature was increased to 70 °C, 76% (GC yield) of desired product **3aa** was obtained with 70% isolated yield. Lowering the temperature or changing the identity of the copper salt had a detrimental effect on the reaction conversion (Table S2, entries 13–23). Control experiments revealed that CuOTf, FeCl₃, and Et₃N are required for our oxyphosphorylation: very little of **3aa** was obtained in their absence (Table 1, entries 4 and 5). Further, when O₂ was replaced by air or N₂, only trace amounts of **3aa** were formed (Table 1, entries 10 and 11) to suggest that O₂ is also an essential prerequisite for this reaction.

Scheme 2. Oxyphosphorylation of Terminal Alkynes with H-Phosphonates under Dioxxygen Atmosphere^a



^aReaction conditions: phenylacetylene **1a** (0.5 mmol), H-phosphonate **2a** (2.0 mmol), CuOTf (5 mol %), FeCl₃ (10 mol %) in DMSO (0.5 M), Et₃N (0.5 mmol), O₂ (balloon), 24 h, all isolated yields.

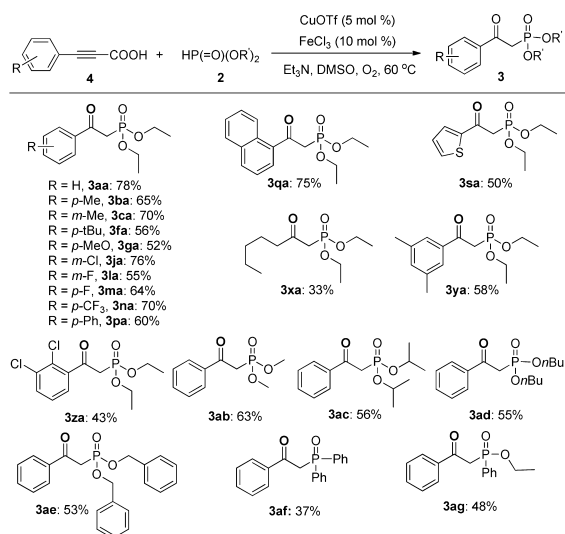
Using the optimal conditions, the substrate scope was investigated (Scheme 2). To our delight, our oxyphosphorylation transforms a range of alkynes and H-phosphonates into β -ketophosphonates. Arylacetylenes possessing either electron-donating or electron-withdrawing substituents were well tolerated in this transformation, affording the desired products in moderate to good yields (**3ba**–**3ra** in Scheme 2). In addition to alkyl and alkoxy groups, halo- and even cyano-substituted arylacetylenes were compatible with the standard conditions. The latter groups can be used to further elaborate the β -ketophosphonate product. Polycyclic and heteroaromatic substituted acetylenes could also be transformed into the corresponding β -ketophosphonates in good to moderate yields. Our oxyphosphorylation reaction tolerates both aliphatic acetylene and internal alkyne substrates (**3ua**–**3va**), albeit with diminished yields. The constraint of our transformation was revealed in diphenylacetylene (**1w**), which produced no product. The scope of our oxyphosphorylation was also surveyed by varying the identity of the H-phosphonate. In addition to diethyl phosphonate (**2a**), we found that dimethyl (**2b**), diisopropyl (**2c**), di-*n*-butyl (**2d**), and dibenzyl phosphates (**2e**) could be used in this oxidative transformation to generate the corresponding β -ketophosphonates **3aa**–**3ae** in good yields (Scheme 2). Most remarkably, both diphenylphosphine oxide (**2f**) and ethyl phenylphosphinate (**2g**) were applicable under the standard conditions as well and produced the desired products **3af** and **3ag** in reasonable yields. The wide scope of both the acetylene and phosphonate partners illustrates the potential of our reaction to efficiently assemble a broad range of functionalized β -ketophosphonates.

Because alkynyl carboxylic acids have no unpleasant smell, are solids, and are easy to handle and store, they have attracted attention in the synthetic community in recent years as terminal acetylene equivalents. To determine if our transformation would be applicable to this class of substrates, phenylpropionic acid was submitted to the reaction conditions, and to our delight, β -ketophosphonate **3aa** was obtained in 72% yield upon isolation. Further screening suggests that amount of H-phosphonate could be reduced to 3 equivalents and the reaction temperature and

time could be reduced to 60 °C and 8 h (Table S6, entry 9, SI). We interpret these results to imply that alkynyl carboxylic acids are more reactive than alkynes in our oxyphosphorylation reaction.

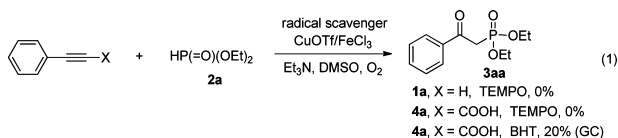
Various alkynyl carboxylic acids and H-phosphonates were investigated to explore the scope of the reaction (Scheme 3).

Scheme 3. Oxyphosphorylation of Alkynyl Carboxylic Acids with H-Phosphonates under Dioxxygen Atmosphere^a



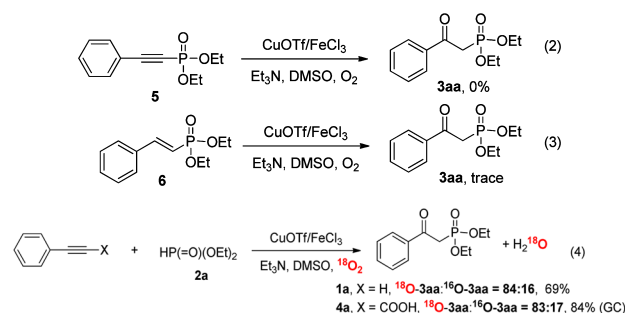
The scope of our transformation mirrored our previous results: a range of electron-releasing and electron-withdrawing aryl- and heteroaryl substituents were tolerated on the propiolic acid component. Similarly, the identity of the H-phosphonate could be changed without attenuating the yield of the oxyphosphorylation reaction. Once again, the transformation underscored the fact that both diphenylphosphine oxide (**2f**) and ethyl phenylphosphinate (**2g**) were well tolerable and the desired products **3af** and **3ag** were obtained in good yields.

In order to elucidate the reaction mechanism, radical trapping experiments were performed (eq 1). First, 2,2,6,6-tetramethyl-1-



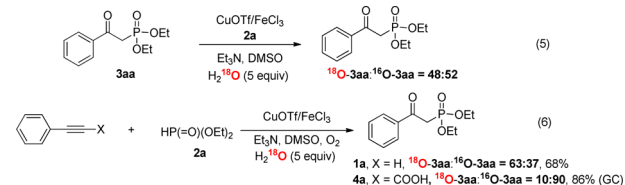
piperidinyloxy (TEMPO) was added along with phenylacetylene or phenylpropionic acid and H-phosphonate under the standard conditions, and inhibition of the reaction was observed. When BHT was employed as the radical scavenger, β -ketophosphonate was produced in 20% yield in GC (eq 1). We interpret these results as evidence that our transformation occurs through a radical mechanism.

Next, diethyl (phenylethynyl)phosphonate (**5**) and (*E*)-diethyl styrylphosphonate (**6**) were prepared according to the literature,^{5,38} and both of them were exposed to the standard conditions. Not surprisingly, no desired β -ketophosphonate **3aa** was obtained (eqs 2 and 3). Thus, coupling with H-phosphonate followed by a Wacker oxidation process was excluded from our transformation as a plausible mechanism.

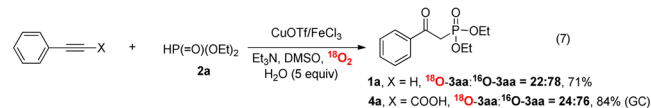


Subsequently, the pivotal nature of dioxxygen to our transformation was investigated (eq 4). We anticipated that using ¹⁸O₂ might enable us to gain insight into the origin of the oxygen of carbonyl group in the β -ketophosphonate. Irrespective of whether phenylacetylene or phenylpropionic acid was used, this isotope-labeling experiment produced the β -ketophosphonate **3aa** where ca. 84% of the ¹⁸O-label was incorporated into the carbonyl.

To determine if incorporation of the label occurred from exchange with water, unlabeled β -ketophosphonate **3aa** was exposed to ¹⁸O-labeled water (H₂¹⁸O), and 48% of ¹⁸O-**3aa** product was detected in the reaction mixture (eq 5), which was consistent to the previous report.²³ Further, when the reaction was conducted in the presence of 5.0 equiv of H₂¹⁸O under O₂, 63% of ¹⁸O-**3aa** and 37% of unlabeled products were detected with alkyne **1a**. In contrast, when alkynyl carboxylic acid **4a** was exposed to 5 equiv of ¹⁸O-labeled water, only 10% of the label was incorporated into **3aa** (eq 6, HRMS spectra in the SI).



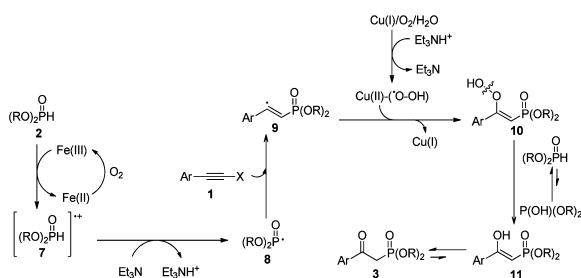
When 5 equiv of unlabeled water was added to the reaction mixture in the presence of ¹⁸O₂, the amount of the label in the β -ketophosphonate product was reduced (eq 7).



In order to better understand the mechanism, EPR (electron paramagnetic resonance) experiments were conducted with phenylacetylene (**1a**) and H-phosphonate **2a** under various reaction conditions with the addition of free-radical spin-trapping agent DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) (see the SI). These experiments unambiguously show that FeCl₃ is vital for the formation of phosphonyl radical³⁹ (Figure S15b-d) and phenylacetylene (**1a**) is both the substrate and trap for this radical in the subsequent reaction under O₂ atmosphere (Figure S15d). Peroxide species was always detected along with sulfinyl radical but with a rather weak EPR signal intensity. Further EPR experiments revealed that the formation of these two radicals was enhanced by CuOTf (Figures S6–S8, S11, SI) irrespective of whether an O₂ atmosphere was present. In sum, these experiments suggest that a portion of peroxide species was generated from water (Figure S11, SI), which coincides with the ¹⁸O-labeled experiments.

On the basis of these results and previous reports,²³ a tentative mechanism for our oxyphosphorylation was constructed

Scheme 4. Plausible Reaction Mechanism of Oxyphosphorylation



(Scheme 4). Single-electron transfer from iron(II) species to HP(=O)(OR)_2 in the presence of molecular oxygen forms dialkyl phosphonate cation radical **7**.^{40,41} Triethylamine deprotonates this cation radical **7** to produce dialkyl phosphonyl radical **8**,⁴² which attacks alkyne to result radical **9**. $\text{Cu(II)-}(\cdot\text{OOH})$ species was generated from Cu(I) under dioxygen atmosphere (with protonated Et_3N). The formed radical **9** trap $\text{Cu(II)-}(\cdot\text{OOH})$ to form hydroperoxide species **10**, which is eventually transformed into the desired product **3**.

In summary, a novel Cu/Fe-co-catalyzed oxyphosphorylation of alkynes or alkynyl carboxylic acids with H-phosphonate has been developed to produce β -ketophosphonates, important intermediates in the Horner–Wadsworth–Emmons (HWE) reaction as well as key intermediates for the synthesis of many biological active compounds in the synthetic community. By employing inexpensive catalysts (copper and iron salts) and using dioxygen as both the oxidant and reactant, our transformation is both sustainable and practical. Our mechanistic studies enable the tentative assignment of a catalytic cycle in which the oxygen in the carbonyl group of β -ketophosphonate originates from both molecular oxygen and water. Experiments aimed at further elucidating the reaction mechanism as well as demonstrating the synthetic application of our reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and spectroscopic data (^1H NMR, ^{13}C NMR, EPR, and HRMS) for the corresponding products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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