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Synthetic Methods

Catalytic and Direct Oxyphosphorylation of Alkenes with Dioxygen and H-Phosphonates Leading to β-Ketophosphonates**

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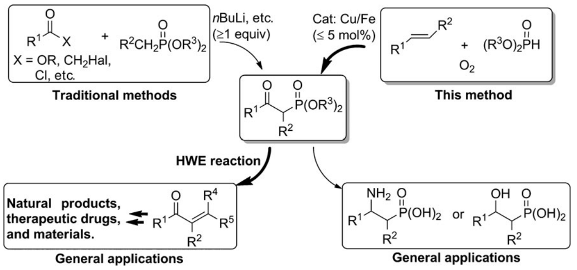
The construction of various types of oxygen-containing organic compounds is a fundamental and important subject in synthetic chemistry. From economic and environmental points of view, the direct use of dioxygen as an oxygen source for functionalization of organic frameworks represents one of the most ideal strategies for constructing oxygen-containing organic materials because of its environmentally benign and sustainable features. Although tremendous efforts have been made in this field during the past several decades,[1] only few convenient and useful transition-metal-catalyzed methods for the incorporation of an oxygen atom from dioxygen into organic substrates have been developed,[1,2] including silver-catalyzed epoxidation of ethylene[3] and cobalt/manganese-catalyzed oxidation of *p*-xylene to terephthalic acid.[4] It is still a challenge to develop direct, efficient, and selective aerobic oxidation systems that possess practical values and distinct reaction mechanisms.

In contrast, alkenes are inexpensive and readily available building blocks, and their difunctionalization has emerged as a fascinating and powerful approach for making valuable products in organic synthesis. Recently, remarkable progress has been made in the transition-metal-catalyzed difunctionalization of alkenes such as dioxygenation,[5] diamination,[6] and aminooxygenation.[7] Herein we report the first catalytic and direct oxyphosphorylation of alkenes with dioxygen and H-phosphonates leading to β-ketophosphonates, an important class of oxygen-containing, synthetic intermediates. The C−P and C=O bonds can be formed in a single operation by the present method.

β-Ketophosphonates are extremely valuable compounds in organic chemistry, especially for the construction of α,β-unsaturated carbonyl compounds through the well-known Horner–Wadsworth–Emmons (HWE) reaction.[8] Furthermore, they can serve as useful precursors in the synthesis of chiral β-amino and β-hydroxy phosphonic acids, both of which are endowed with interesting biological properties.[9] In addition, β-ketophosphonates also exhibit a wide range of biological activities[10] and outstanding metal-complexing abilities (Scheme 1).[11] Generally, β-ketophosphonates are prepared by the reaction of α-haloketones with trialkylphosphites (Arbuzov reaction)[12] or acylation of alkylphosphonates with carboxylic acid derivatives by employing stoichiometric amounts of organometallic reagents (Scheme 1).[13] Alternative procedures include oxidation of β-hydroxyalkylphosphonates with stoichiometric amounts of inorganic oxidants,[14] acylation of arenes with phosphonoacetic acids,[15] and metal-mediated reactions of α-halophosphonates with esters.[16] However, almost all of these methods suffer from limitations such as low atom economy, poor substrate scope, tedious procedures, relatively harsh reaction conditions, or requiring excess amounts of organometallic reagents. Therefore, the development of mild, convenient, efficient, and especially, environmentally benign methods to access β-ketophosphonates is still highly desirable in synthetic chemistry.



Scheme 1. Synthetic methods and general applications of β-ketophosphonates.

The present method of the copper/iron cocatalyzed oxidative synthesis of β-ketophosphonates by direct difunctionalization of alkenes with dioxygen and H-phosphonates (Scheme 1), to the best of our knowledge, is the first example of transition-metal-catalyzed direct synthesis of β-ketophosphonates from simple and commercially available starting materials, and does not require the use of stoichiometric amounts of organometallic reagents and cryogenics.

Initially, under an oxygen atmosphere, the reaction of styrene (**1a**) with $(i\mathrm{PrO})_2\mathrm{P(O)H}$ (**2a**) was performed to examine the catalytic activity of various transition-metal complexes including Au, Ag, Cu, Ru, Rh, Ni, Pd, Pt, Bi, In, Ti, and Fe salts (see Table S1 in the Supporting Information). Among the above-mentioned metal salts examined, copper salts, especially $\mathrm{CuBr_2}$, was found to be the most effective catalyst to generate the desired product **3aa** (Table 1, entries 1–4); in contrast other metal salts such as $\mathrm{FeBr_3}$ and $\mathrm{RuBr_3{\cdot}3H_2O}$ only gave the product **3aa** in very low yield

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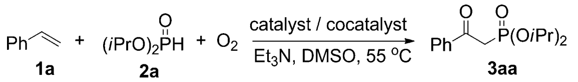
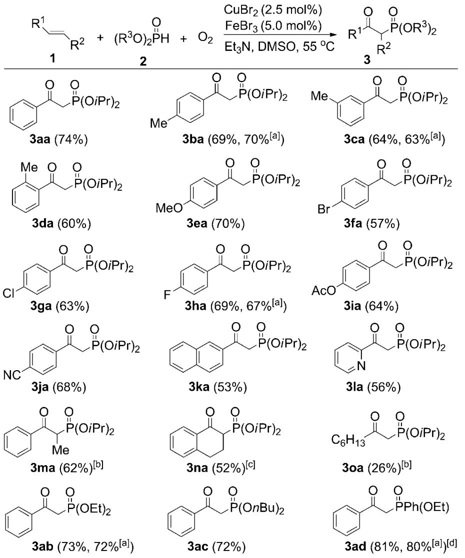
Table 1: Oxyphosphorylation of alkenes to form β-ketophosphonate: Optimization of reaction conditions.[a]



Entry	Catalyst	Cocatalyst	Yield [%][b]
1	CuI	–	14
2	CuBr	–	30
3	$CuCl_2$	–	43
4	$CuBr_2$	–	44
5	$FeBr_3$	–	6
6	$RuBr_3 \cdot 3\,H_2O$	–	6
7	$CuBr_2$ (20 mol %)	–	32
8	$\mathbf{CuBr_2}$	$\mathbf{FeBr_3}$	**74**
9	$CuBr_2$	$FeCl_3$	72
10	$CuCl_2$	$FeCl_3$	70
11	$CuBr_2$	$RuBr_3 \cdot 3\,H_2O$	60
12	$CuBr_2$	$ZnBr_2$	41
13	$CuBr_2$	$AlBr_3$	50
14	$CuBr_2$	$AuCl_3$	49
15	$CuBr_2$	$MgBr_2 \cdot 6\,H_2O$	48
16	$CuBr_2$	$BiBr_3$	60
17	$CuBr_2$	$InBr_3$	55
18	$CuBr_2$	$FeBr_3$	64[c]
19	–	–	n.r.
20	$CuBr_2$	$FeBr_3$	n.r.[d]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), catalyst (2.5 mol %), cocatalyst (5.0 mol %), Et_3N (0.5 mmol), DMSO (1 mL), O_2 (balloon), 24 h. [b] Yields of isolated products based on **1a**. [c] Under air. [d] Under N_2. DMSO = dimethyl sulfoxide, n.r. = no reaction.



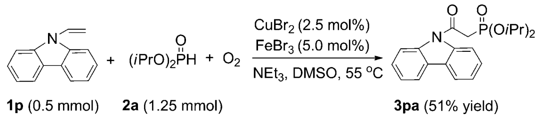
Scheme 2. Products obtained by the copper/iron cocatalyzed oxyphosphorylation of alkenes with dioxygen and H-phosphonates. Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), $CuBr_2$ (2.5 mol %), $FeBr_3$ (5.0 mol %), Et_3N (0.5 mmol), DMSO (1 mL), O_2 (balloon), 24 h. Yields of isolated products are based on **1**. [a] Catalyst: $CuCl_2$ (2.5 mol %), $FeCl_3$ (5.0 mol %). [b] **2** (1.25 mmol), 48 h. [c] **2** (1.25 mmol), 12 h. [d] Hydrogen ethyl phenylphosphinate (1 mmol), 24 h.

(Table 1, entries 5 and 6). An increase in the $CuBr_2$ loading did not improve this oxyphosphorylation reaction, and a high loading (20 mol %) led to a decrease of the yield (Table 1, entry 7). Gratifyingly, further exploration suggested that a good yield of **3aa** was obtained when $FeBr_3$ or $FeCl_3$ was employed as an additive (Table 1, entries 8 and 9). Notably, the combination of cheaper $CuCl_2$ with $FeCl_3$ also gives the product **3aa** in good yield (Table 1, entry 10). Other Lewis acid additives including $RuBr_3 \cdot 3\,H_2O$, $ZnBr_2$, $AlBr_3$, $AuCl_3$, $MgBr_2 \cdot 6\,H_2O$, $BiBr_3$, and $InBr_3$ were less effective (Table 1, entries 11–17). The addition of a base was critical to the success of this oxyphosphorylation reaction and no product was detected in the absence of a base. Among the various bases screened, Et_3N turned out to be the best choice, while others such as DBU (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene), $i\text{Pr}_2\text{NEt}$, Et_2NH, pyridine, Cs_2CO_3, and Na_2CO_3 were less effective (see Table S2 in the Supporting Information). After an extensive screening of the reaction parameters (see Table 1 and the Supporting Information), the best yield of **3aa** (74 %) was obtained by employing 2.5 mol % $CuBr_2$, 5.0 mol % $FeBr_3$, and 1.0 equivalent of Et_3N in DMSO at 55 °C under an oxygen atmosphere (Table 1, entry 8). Notably, a 64 % yield could also be obtained even under an air atmosphere (Table 1, entry 18). No product was detected when the reaction was performed in the absence of the catalyst or O_2 (Table 1, entries 19 and 20).

Under the optimized reaction conditions, the substrate scope of this reaction was investigated. As demonstrated in Scheme 2, a variety of β-ketophosphonates can be conveniently and efficiently obtained by this novel copper/iron cocatalyzed oxyphosphorylation reaction of alkenes. In general, both electron-rich and electron-deficient aromatic alkenes were suitable for this protocol, and the corresponding oxidative coupling products were obtained in moderate to good yields (**3aa**–**3ka**). Heteroaromatic alkenes such as 2-vinylpyridine could also be used in the reaction to give the expected β-ketophosphonate **3la** in 56 % yield. Notably, internal aromatic alkenes were tolerated in this process, thus leading to the desired products in moderate yields (**3ma** and **3na**). Nevertheless, when an aliphatic alkene such as 1-octene was used as the substrate, the corresponding product was obtained in relatively low yield (**3oa**).

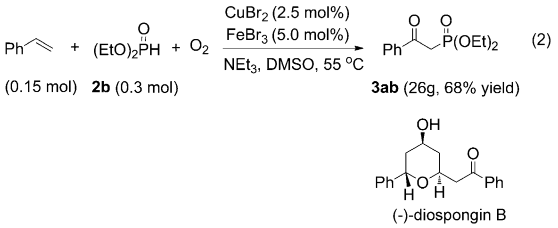
With respect to the H-phosphonates, in addition to **2a**, diethyl and dibutyl phosphonates were all suitable substrates, and generated the corresponding products **3ab** and **3ac** in good yields. In addition, hydrogen ethyl phenylphosphinate could also be transformed to the corresponding β-ketophosphinate **3ad** in high yield.

Interestingly, an enamine such as 9-vinylcarbazole was also compatible with this reaction, thus affording the corresponding product **3pa** in 51 % yield [Eq. (1)].



(1)

It is worth noting that the reaction can also be effectively scaled up with the similar efficiency. For example, the reaction of styrene (**1a**, 0.15 mol) with $(EtO)_2P(O)H$ (**2b**, 0.3 mol) gave the corresponding β-ketophosphonate **3ab** in 68 % yield (26 g). Significantly, **3ab** is a key intermediate for the synthesis of various natural products such as (−)-diospongin B, which shows conspicuous antiosteoporotic activity for the treatment of osteoporosis [Eq. (2)].[17]



In conclusion, we have successfully developed the first catalytic oxidative synthesis of β-ketophosphonates through direct oxyphosphorylation of alkenes with dioxygen and H-phosphonates under mild reaction conditions. This reaction can be effectively scaled up and more than 20 grams of product were conveniently obtained in a one-pot process. Preliminary mechanistic studies indicated that the carbonyl oxygen atom of β-ketophosphonates originated from the dioxygen and this reaction might involve a radical process.[18] The present protocol, which utilizes dioxygen as the oxidant and oxygen source, and cheap copper/iron salts as catalysts, provides not only a green and attractive approach to β-ketophosphonates, but also a useful example of direct incorporation of oxygen atom from dioxygen into organic frameworks. Further mechanistic details and synthetic applications are now under investigation.

Experimental Section

The experimental procedure for multigram-scale reaction: Styrene (15.6 g, 0.15 mol) was added to a mixture of H-diethyl phosphonate (41.4 g, 0.3 mol), CuBr$_2$ (0.83 g, 3.8 mmol, 2.5 mol %), FeBr$_3$ (2.2 g, 7.5 mmol, 5.0 mol %), and Et$_3$N (21 mL, 0.15 mol) in DMSO (50 mL) at room temperature under O$_2$ (balloon). The reaction mixture was stirred at 55 °C for 48 h. After completion of the reaction, water (100 mL) was added to the reaction mixture, and the resulting mixture was extracted with dichloromethane. The organic layer was washed with 0.1 N L^{-1} HCl (1 × 100 mL), water (3 × 100 mL), brine (100 mL × 1), and the separated aqueous phase was extracted with CH$_2$Cl$_2$ (100 mL × 2). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to afford the β-ketophosphonate **3ab** as a light yellow oil (26.0 g, 68 %).

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