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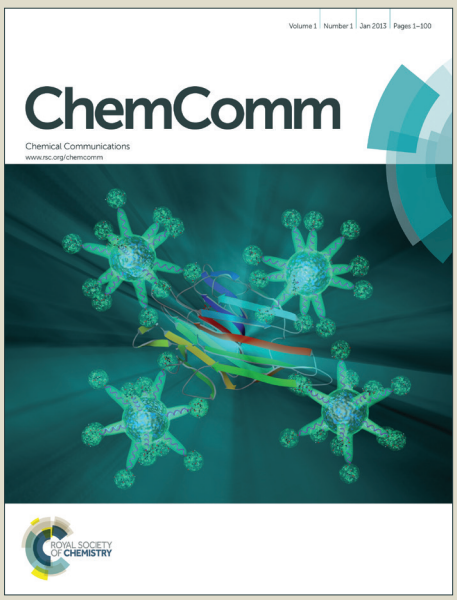

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Copper-Catalyzed Tandem Phosphination-Decarboxylation-Oxidation of Alkynyl Acids with H-Phosphine Oxides: A Facile Synthesis of β-Ketophosphine Oxides

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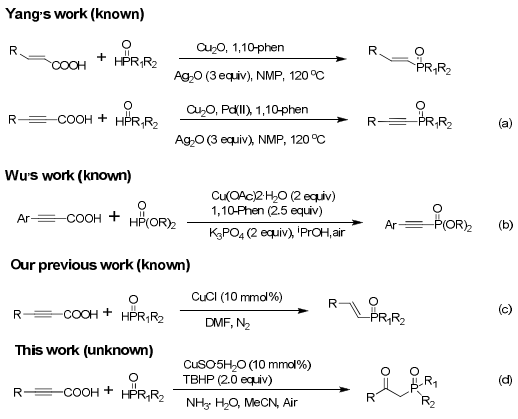
The general method for the tandem phosphination-decarboxylation-oxidation of alkynyl acids under aerobic conditions has been developed. In the presence of $CuSO_4 \cdot 5H_2O$ and TBHP, the reactions provide a novel access to β-ketophosphine oxides in good to excellent yields. This transformation allows the direct formation of a P-C bond and the construction of a keto group in one reaction.

Organophosphorus compounds have broad applications in the fields of organic synthesis, [1] materials,[2] medicinal chemistry,[3] and ligand chemistry.[4] Thus, to develop new efficient method for C–P bond construction has attracted increasing attention. β-ketophosphine oxides can facilitate carbon–carbon bond formation and then the diphenylphosphinyl group can be easily removed to give olefins,[5] cyclopropanes,[6] and branched ketones.[7] β-ketophosphine oxides can also be used for liquid-liquid extraction of metal ions because of their prominent metal-complexing abilities.[8] The traditional methods to prepare β-ketophosphine oxides are based on the acylation of alkyl phosphine oxides with carboxylic acid derivatives which employ stoichiometric amounts of the hazardous organometallic reagents.[9] In recent years, our group[10] and other researchers[11] reported many practical approaches to β-ketophosphonates, but these methods are not ideal choices for the synthesis of β-ketophosphine oxides.

In 1966, Nilsson reported the pioneering work of decarboxylative coupling.[12] Since 2002, a series of transition-metal-catalyzed decarboxylative C−C and C−heteroatom bonds formation reactions have been extensively developed.[13] Compared with the traditional cross-couplings and C–H activation, decarboxylative coupling reactions using carboxylic acid derivatives have several advantages. Instead of metal waste from organometallic coupling reagents, less toxic carbon dioxide is released as a byproduct after the complete conversion, which reduces the cost of the process for the treatment of waste. It is noteworthy that as a practical alternative, the use of arylpropiolic acids as terminal arylacetylene surrogates is safer and more attractive because arylpropiolic acids are usually solids without an unpleasant smell and are convenient to synthesize, store, and transport. On the basis of this viewpoint, Wu's group fulfilled the decarboxylative coupling of arylpropiolic acids with P(O)H to construct a Csp-P bond with the assistance of a copper catalyst system.[14] Recently, our group developed an efficient synthesis of *E*-alkenylphosphine oxides via copper-catalyzed decarboxylative cross-coupling of alkynyl acids with H-phosphine oxides.[15] To the best of our knowledge, the example of β-ketophosphine oxide formation via decarboxylative coupling of alkynyl acids has yet to be reported.

Reactions involving organophosphorus radicals have a long history, and are useful reactive species in organic synthetic chemistry.[16] Owing to our continuous interests in the P−C bond formation[17] and the reaction of organophosphorus radicals,[18] we present herein our recent progress in constructing valuable β-ketophosphine oxides via tandem phosphination-decarboxylation-oxidation of alkynyl acids. This transformation allows the direct formation of a P-C bond and the construction of a keto group in one reaction via a radical process.



Scheme 1. C−P bond formation via decarboxylative coupling.

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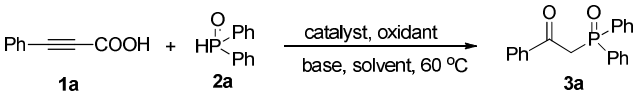
Table 1. Reaction conditions optimization.[a]



Entry	Catalyst	Base[b]	Solvent	Oxidant	Yield[c] (%)
1	$CuSO_4·5H_2O$	$NH_3·H_2O$	MeCN	air	43
2	CuBr	$NH_3·H_2O$	MeCN	air	14
3	$CuBr_2$	$NH_3·H_2O$	MeCN	air	43
4	Cu_2O	$NH_3·H_2O$	MeCN	air	25
5	CuO	$NH_3·H_2O$	MeCN	air	37
6	CuI	$NH_3·H_2O$	MeCN	air	trace
8	CuCl	$NH_3·H_2O$	MeCN	air	trace
9	$Cu(OTf)_2$	$NH_3·H_2O$	MeCN	air	40
10	$CuSO_4·5H_2O$	-	MeCN	air	26
11	$CuSO_4·5H_2O$	Cs_2CO_3	MeCN	air	25
12	$CuSO_4·5H_2O$	K_2CO_3	MeCN	air	33
13	$CuSO_4·5H_2O$	NaOAc	MeCN	air	33
14	$CuBr_2$	$(iPr)_2NEt$	MeCN	air	trace
15	$CuBr_2$	Et_3N	MeCN	air	18
16	$CuBr_2$	pyridine	MeCN	air	6
17	$CuSO_4·5H_2O$	$NH_3·H_2O$	MeCN	H_2O_2	12
18	***$CuSO_4·5H_2O$***	***$NH_3·H_2O$***	***MeCN***	***TBHP***	***90***
19	$CuSO_4·5H_2O$	$NH_3·H_2O$	MeCN	BQ	16
20	$CuSO_4·5H_2O$	$NH_3·H_2O$	MeCN	$K_2S_2O_8$	48
21	$CuSO_4·5H_2O$	$NH_3·H_2O$	MeCN	DTBP	trace
22	$CuSO_4·5H_2O$	$NH_3·H_2O$	MeCN	O_2	30
23	$CuSO_4·5H_2O$	$NH_3·H_2O$	DMF	TBHP	24
24	$CuSO_4·5H_2O$	$NH_3·H_2O$	DMSO	TBHP	56
25	$CuSO_4·5H_2O$	$NH_3·H_2O$	EtOH	TBHP	52
26	$CuSO_4·5H_2O$	$NH_3·H_2O$	1,4-dioxane	TBHP	28
27	-	$NH_3·H_2O$	MeCN	TBHP	0
28	$CuSO_4·5H_2O$	$NH_3·H_2O$	MeCN	TBHP	80[d](5)[e]
29[f]	$CuSO_4·5H_2O$	$NH_3·H_2O$	MeCN	TBHP	70

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), catalyst (10 mol %), base, oxidant, solvent (1.5 mL) in an open flask at 60 °C for 2 h. [b] Unless otherwise specified, $NH_3·H_2O$ (25%) was 0.25 mL, other bases were 0.4 mmol. [c] Yields were determined by ^1H NMR. [d] At 70 °C. [e] At room temperature. [f] **2a** (0.4 mmol).

At the outset of our investigation, phenylpropiolic acid (**1a**) and $H(O)PPh_2$ (**2a**) were chosen as the model substrates to survey the reaction conditions. Gratifyingly, when a mixture of **1a** (0.2 mmol), **2a** (0.8 mmol), $CuSO_4·5H_2O$ (0.02 mmol) and $NH_3·H_2O$ (25%, 0.25 mL) in MeCN was heated to 60 °C under air for 2 h, the desired product **3a** was obtained in 43% yield (Table 1, entry 1). Subsequently, various Cu(I) and Cu(II) salts were further checked and the results showed that Cu(II) salts were more effective to give the desired product (entries 1-9). A brief survey of bases such as Cs_2CO_3, K_2CO_3, NaOAc, $(iPr)_2NEt$, NEt_3, pyridine, and $NH_3·H_2O$ (25%) led to the observation that $NH_3·H_2O$ (25%) gave the highest yield of **3a** (entries 9-16). In our previous synthesis of a-hydroxy phosphonates from H-phosphonates and alcohols, we found that the combination use of Cu(II) and TBHP (tert-butylhydroperoxide) could promote the reaction efficiently.[16h] Gratifyingly, the yield increased tremendously when TBHP was employed as oxidant. However, the other oxidants like $K_2S_2O_8$, BQ (p-benzoquinone), DTBP (di-tert-butyl peroxide), and H_2O_2 did not improve the yield (entries 17-22). The solvent systems employed also notably affected the related reaction efficiencies. Conducting the reaction in EtOH, DMF, DMSO and 1,4-dioxane gave the product **3a** in very low yield (entries 23-26), while the reaction conducted in MeCN gave a high yield (entry 18). Moreover, the yield was reduced to 30% using O_2 instead of TBHP (entry 22). No desired product was afforded without copper salt (entry 27). The yield of product **3a** decreased when the temperature was raised to 70 °C or decreased to room temperature (entry 28). However, the attempt to decrease the amount of **2a** was failed (entry 29). After optimization of the reaction conditions, we established a highly efficient route to the tandem decarboxylation-phosphination-oxidation of alkynyl acids (entry 18).

With this preliminary result in hand, the generality of the method was explored under the optimized conditions [alkynyl acid (0.2 mmol), P(O)-H (0.8 mmol), $CuSO_4·5H_2O$ (10 mmol %), TBHP (2 equiv), $NH_3·H_2O$ (25%, 0.25 mL) in MeCN at 60 °C under air for 2 h], and the results are summarized in Table 2. In general, a variety of functional groups on the phenyl ring of arylpropiolic acids were compatible under this procedure, affording the desired products in good to excellent yields. The methyl substituted arylpropiolic acids, such as *meta*-methyl, *para*-methyl, and 3,5-dimethyl groups on the aryl ring, reacted with **2a** efficiently and gave the desired products **3c-3e** in high yields. The *ortho*-substituted arylpropiolic acids exhibited a particularly distinct steric hindrance effect (**3b**–**3e**), and the corresponding β-ketophosphine oxide **3b** was obtained in a slightly lower yield (75%). Halogen atoms such as fluoro, chloro, bromo, and iodo on the aromatic ring were unaffected under the present reaction conditions to afford the corresponding products **3f-3j** in good yields, which could allow for further synthetic transformations. Arylpropiolic acids bearing electron-withdrawing CF_3, COOEt, CN groups reacted smoothly to give the corresponding products in good yields (**3k-3n**). Treatment of diphosphine oxide with methoxy-substituted arylpropiolic acid led to the formation of product **3o** in 50% yield. Replacing methoxy group with trifluoromethoxy group resulted in a higher yield (**3p**, 87%). More bulky substrates such as 3-(naphthalen-1-yl)propiolic acid also smoothly reacted with diphosphine oxide and gave product **3q** in 56% yield. In addition, 3-(thiophen-2-yl)propiolic acid could also provide the expected product **3s** in 46% yield.

The substrate scope was further investigated by reacting phenylpropiolic acid (**1a**) with different organophosphorous reagents. Apart from **2a**, di-p-tolylphosphine oxide (**2b**) and bis(4-chlorophenyl)phosphine oxide (**2c**) were all suitable substrates, generating the corresponding products **3t** and **3u** in 86% and 65% yields, respectively. However, diarylphosphine oxide involving a para-bromo substituent **2d** produced the desired product **3v** in only 43% yield. The butyl(p-tolyl)phosphine oxide (**2e**) also efficiently reacted with **1a** and led to the corresponding product **3w** in 89% yield. Treatment of ethyl phenylphosphinate (**2f**) with **1a** afforded the desired product **3x** in a lower yield of 42%. When diethyl phosphonate (**2g**) was used, an only 22% yield of β-ketophosphonate **3y** was obtained. Alkynyl acid was also examined. Unfortunately, only trace amount of the desired product was detected by ^{31}P NMR.

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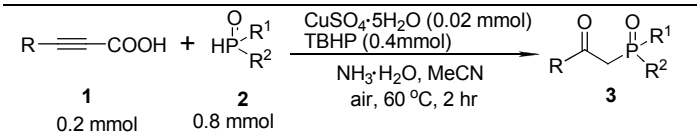
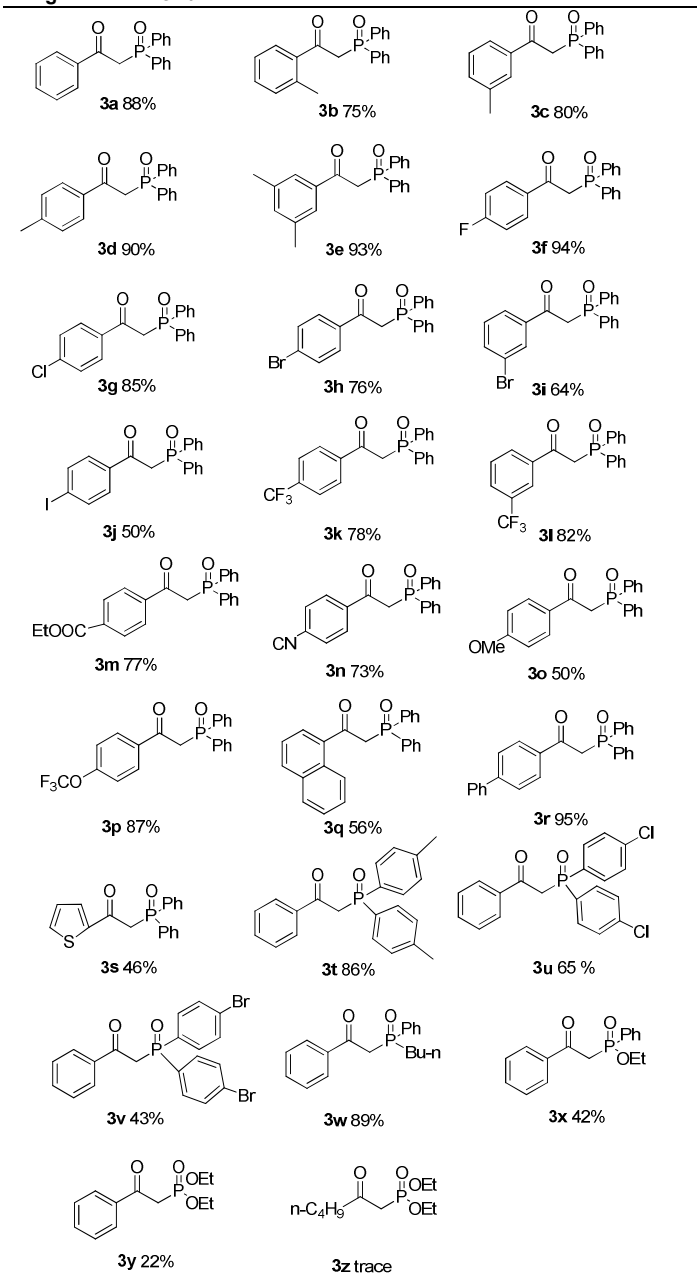
Table 2. Reaction of P(O)-H compounds with alkynyl acids.

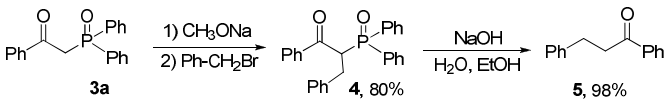


1 0.2 mmol **2** 0.8 mmol **3**

2a: $R^1 = R^2 = C_6H_4$ **2b**: $R^1 = R^2 = 4\text{-}MeC_6H_4$ **2c**: $R^1 = R^2 = 4\text{-}ClC_6H_4$
2d: $R^1 = R^2 = 4\text{-}BrC_6H_4$ **2e**: R^1 = n-Bu $R^2 = C_6H_4$ **2f**: R^1 = OEt $R^2 = C_6H_4$
2g: $R^1 = R^2$ = OEt

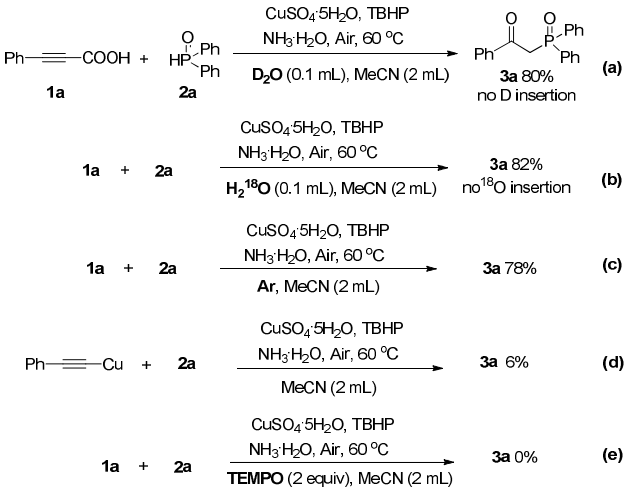


With the synthetic β-ketophosphine oxides in hand, we next prepared α-benzyl β-ketodiphenylphosphine oxide **4** from benzyl bromide and **3a** in good yield, which was converted into 1,3-diphenylpropan-1-one **5** in 98% yield via a dephosphinoylation process (Scheme 2).

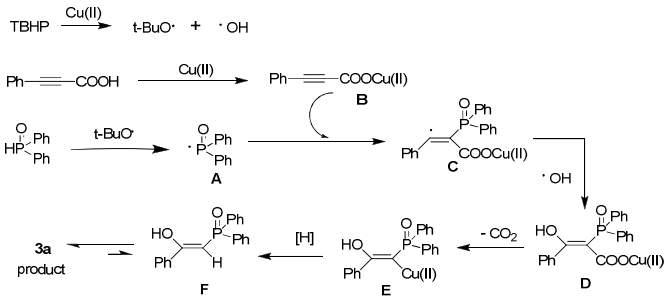


Scheme 2. Synthesis of 1,3-diphenylpropan-1-one.

In an effort to improve our understanding of the reaction profile, a series of isotope labeling studies were conducted. When $H_2{}^{18}O$ or D_2O was added to the reaction mixture under the optimal conditions, no isotope-labeled product was detected by ^1H NMR and ESI-MS spectrum (Scheme 3, **a** and **b**). In the absence of air, the transformation could still proceed smoothly to provide **3a** in a good yield of 78% (Scheme 3, **c**). It was suggested that the oxygen of the newly formed carbonyl group of **3a** mainly originated from TBHP. When **2a** was treated with 1.2 equiv of (phenylethynyl)copper under the optimized reaction condition, only a trace amount of the desired product was observed, illustrating that (phenylethynyl)copper might not be a intermediate in this process (**d**). A radical scavenger such as TEMPO could completely restrain the reaction, thus suggesting that the radical processes might be involved. Based on these experimental results and previous mechanistic studies, a plausible mechanism is proposed as shown in Scheme 4.



Scheme 3. Experiments for the mechanistic study.



Scheme 4. Proposed reaction mechanism.

First, TBHP generates the tert-butoxy radical and hydroxyl radical in the presence of Cu(II). Then, tert-butoxy radical triggers

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the phosphorus radical **A** formation from $H(O)PPh_2$. Reaction of the phenylpropiolic acid with Cu(II) generates a salt of cupric carboxylate **B**. Subsequently, addition of phosphorus radical **A** to the α-position of the triple bond of **B** gives intermediate **C**, which is ultimately trapped by hydroxyl radical to form intermediate **D**. Then **D** release one molecular CO_2 to produce alkenyl copper intermediate **E**. Finally, the protonolysis of intermediate lead to the formation of **F**, which isomerizes and affords the desired product.

In conclusion, we have successfully developed the first facile method for the preparation of β-ketophosphine oxides via decarboxylation-phosphination-oxidation of various alkynyl acids with H-phosphine oxides. Importantly, this transformation would provide a new pathway for formation of Csp^3-P and C=O bonds in one step. This method is highly efficient and provides a rapid access to a broad spectrum of β-ketophosphine oxides in good to excellent yields. Moreover, the use of inexpensive $CuSO_4 \cdot 5H_2O$ catalyst, using readily available alkynyl acids only producing CO_2 mean that this facile protocol will be attractive for academia and industry.

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Electronic Supplementary Information (ESI) available: Experimental procedures for the synthesis, spectral data and NMR spectra of compounds **3a**-**3z**. See DOI: 10.1039/c000000x/

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