



Cite this: *Chem. Commun.*, 2015, 51, 7839

Received 6th March 2015,
Accepted 31st March 2015

DOI: 10.1039/c5cc01904d

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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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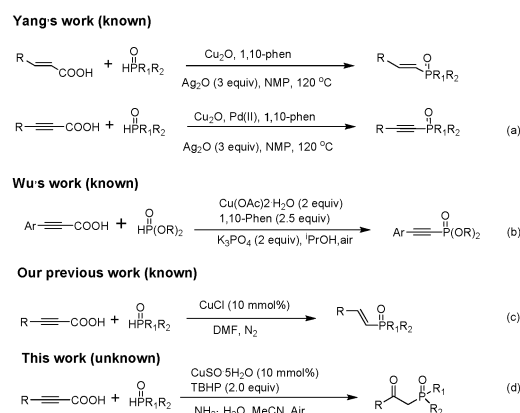
The general method for the tandem phosphination–decarboxylation–oxidation of alkynyl acids under aerobic conditions has been developed. In the presence of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and TBHP, the reactions provide a novel access to β -ketophosphine oxides in good to excellent yields. This 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 science,² medicinal chemistry,³ and ligand chemistry.⁴ Thus, development of a 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 group¹⁰ and other researchers¹¹ 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 bond formation reactions have been extensively developed.¹³ Compared with the traditional cross-coupling reactions 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 arylpropionic acids as terminal arylacetylene surrogates is safer and more attractive because arylpropionic 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 arylpropionic 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 is yet to be reported (Scheme 1).

Reactions involving organophosphorus radicals have a long history, and are useful reactive species in organic synthetic chemistry.¹⁶ Owing to our continuous interest in the P–C bond formation¹⁷ and the reaction of organophosphorus radicals,¹⁸ we present herein our recent progress in constructing valuable



Scheme 1 C–P bond formation *via* decarboxylative coupling.

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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/c5cc01904d



Table 1 Reaction condition optimization^a

Entry	Catalyst	Base ^b	Solvent	Oxidant	Yield ^c (%)
1	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	MeCN	Air	43
2	CuBr	NH ₃ ·H ₂ O	MeCN	Air	14
3	CuBr ₂	NH ₃ ·H ₂ O	MeCN	Air	43
4	Cu ₂ O	NH ₃ ·H ₂ O	MeCN	Air	25
5	CuO	NH ₃ ·H ₂ O	MeCN	Air	37
6	CuI	NH ₃ ·H ₂ O	MeCN	Air	Trace
8	CuCl	NH ₃ ·H ₂ O	MeCN	Air	Trace
9	Cu(OTf) ₂	NH ₃ ·H ₂ O	MeCN	Air	40
10	CuSO ₄ ·5H ₂ O	—	MeCN	Air	26
11	CuSO ₄ ·5H ₂ O	K ₂ CO ₃	MeCN	Air	25
12	CuSO ₄ ·5H ₂ O	K ₂ CO ₃	MeCN	Air	33
13	CuSO ₄ ·5H ₂ O	NaOAc	MeCN	Air	33
14	CuBr ₂	(iPr) ₂ NEt	MeCN	Air	Trace
15	CuBr ₂	Et ₃ N	MeCN	Air	18
16	CuBr ₂	Pyridine	MeCN	Air	6
17	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	MeCN	H ₂ O ₂	12
18	CuSO₄·5H₂O	NH₃·H₂O	MeCN	TBHP	90
19	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	MeCN	BQ	16
20	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	MeCN	K ₂ S ₂ O ₈	48
21	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	MeCN	DTBP	Trace
22	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	MeCN	O ₂	30
23	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	DMF	TBHP	24
24	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	DMSO	TBHP	56
25	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	EtOH	TBHP	52
26	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	1,4-Dioxane	TBHP	28
27	—	NH ₃ ·H ₂ O	MeCN	TBHP	0
28	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	MeCN	TBHP	80 ^{d(5)} ^e
29 ^f	CuSO ₄ ·5H ₂ O	NH ₃ ·H ₂ O	MeCN	TBHP	70

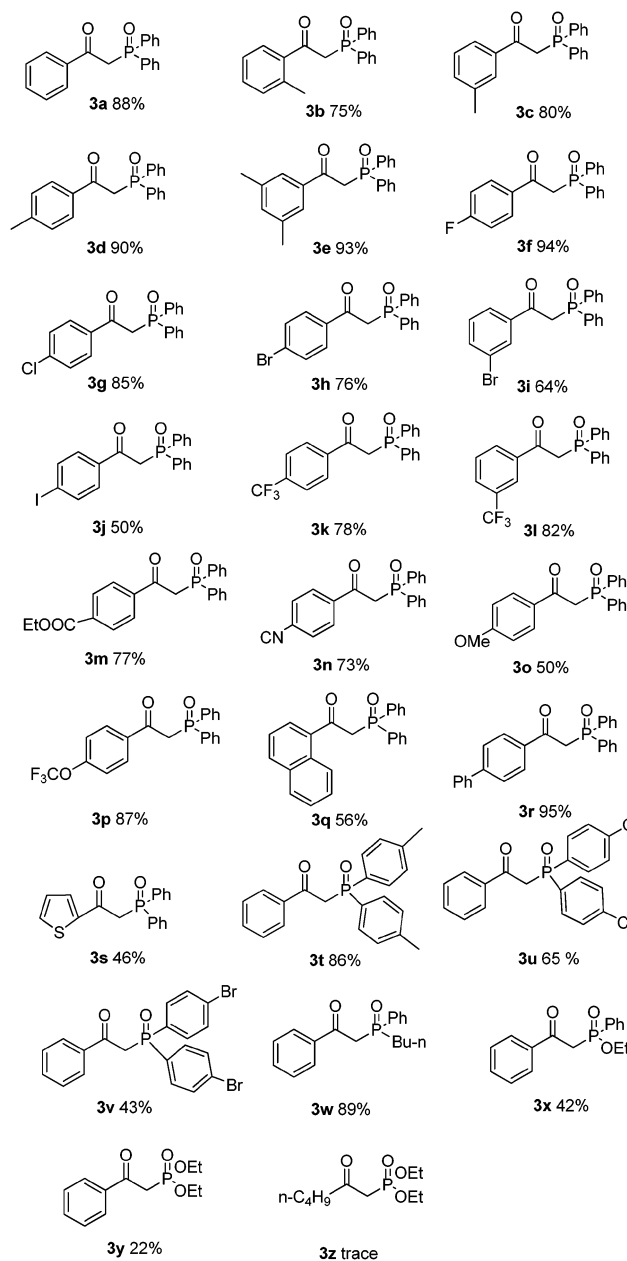
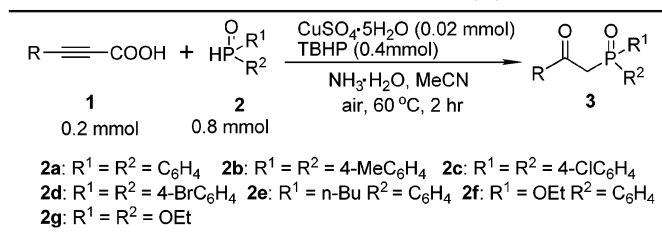
^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), catalyst (10 mol%), base, oxidant, solvent (1.5 mL) in an open flask at 60 °C for 2 h. ^b Unless otherwise specified, NH₃·H₂O (25%) was 0.25 mL, other bases were 0.4 mmol. ^c Yields were determined by ¹H NMR. ^d At 70 °C. ^e At room temperature. ^f **2a** (0.4 mmol).

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.

At the outset of our investigation, phenylpropionic acid (**1a**) and H(O)PPH₂ (**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), CuSO₄·5H₂O (0.02 mmol) and NH₃·H₂O (25%, 0.25 mL) in MeCN was heated to 60 °C in 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 Cs₂CO₃, K₂CO₃, NaOAc, (iPr)₂NEt, NEt₃, pyridine, and NH₃·H₂O (25%) led to the observation that NH₃·H₂O (25%) gave **3a** in the highest yield (entries 9–16). In our previous synthesis of α-hydroxy phosphonates from H-phosphonates and alcohols, we found that the combined use of Cu(II) and TBHP (*tert*-butylhydroperoxide) could promote the reaction efficiently.^{16h} Gratifyingly, the yield increased tremendously when TBHP was employed as an oxidant. However, the other oxidants like K₂S₂O₈, BQ (*p*-benzoquinone), DTBP (di-*tert*-butyl peroxide), and H₂O₂ 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% when using O₂ instead of TBHP (entry 22). No desired product was afforded without copper salts (entry 27). The yield of product **3a** decreased when

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



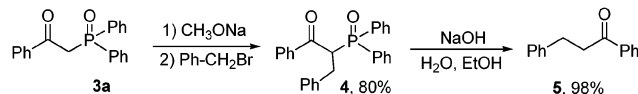
the temperature was raised to 70 °C or decreased to room temperature (entry 28). However, the attempt to decrease the amount of **2a** failed (entry 29). After optimization of the reaction conditions, we established a highly efficient route to the tandem decarboxylation–phosphination–oxidation of alkynyl 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), CuSO₄·5H₂O (10 mmol%), TBHP (2 equiv.), NH₃·H₂O (25%, 0.25 mL) in MeCN at 60 °C in air for 2 h], and the results are summarized in Table 2. In general, a variety of functional groups on the phenyl ring of arylpropionic acids were compatible using this procedure, affording the desired products in good to excellent yields. The methyl substituted arylpropionic 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 arylpropionic 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. Arylpropionic acids bearing electron-withdrawing CF₃, COOEt, CN groups reacted smoothly to give the corresponding products in good yields (**3k–3n**). Treatment of diphosphine oxide with methoxy-substituted arylpropionic acid led to the formation of product **3o** in 50% yield. Replacing the methoxy group with the trifluoromethoxy group resulted in a higher yield (**3p**, 87%). More bulky substrates such as 3-(naphthalen-1-yl)propionic acid also smoothly reacted with diphosphine oxide and gave product **3q** in 56% yield. In addition, 3-(thiophen-2-yl)propionic acid could also provide the expected product **3s** in 46% yield.

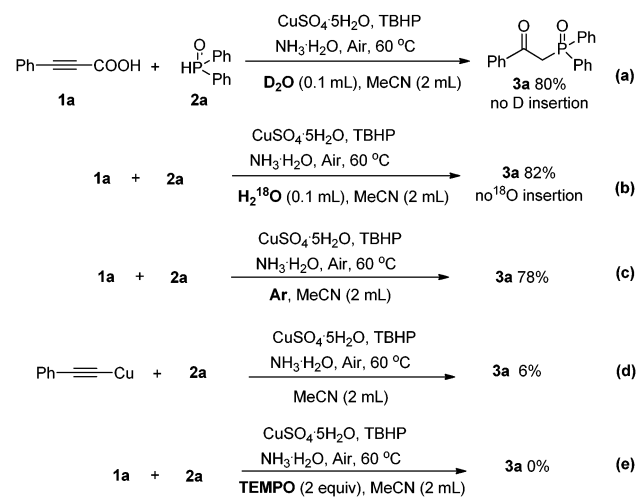
The substrate scope was further investigated by reacting phenylpropionic acid (**1a**) with different organophosphorous reagents. Apart from **2a**, di-*p*-tolylphosphine oxide (**2b**) and bis(4-chlorophenyl)phosphine oxide (**2c**) were all suitable substrates, generating the corresponding products **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, β-ketophosphonate **3y** was obtained in only 22% yield. Alkynyl acid was also examined. Unfortunately, only a trace amount of the desired product was detected by ³¹P NMR analysis.

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).

In an effort to improve our understanding of the reaction profile, a series of isotope labeling studies were conducted. When H₂¹⁸O or D₂O was added to the reaction mixture under



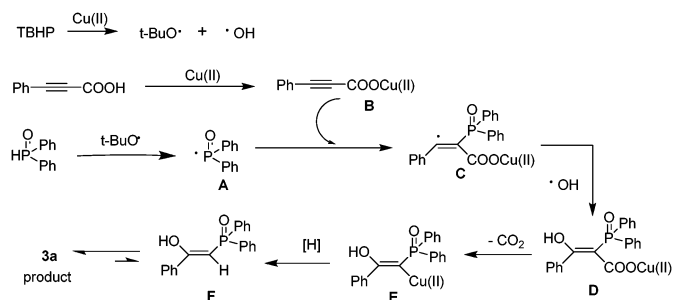
Scheme 2 Synthesis of 1,3-diphenylpropan-1-one.



Scheme 3 Experiments for the mechanistic study.

the optimal conditions, no isotope-labeled product was detected in ¹H NMR and ESI-MS spectra (Scheme 3a and b). In the absence of air, the transformation could still proceed smoothly to provide **3a** in a good yield of 78% (Scheme 3c). 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 conditions, only a trace amount of the desired product was observed, illustrating that (phenylethynyl)copper might not be an 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.

First, TBHP generates the *tert*-butoxy radical and the hydroxyl radical in the presence of Cu(II). Then, the *tert*-butoxy radical triggers the formation of phosphorus radical **A** from H(O)PPH₂. Reaction of the phenylpropionic acid with Cu(II) generates a salt of cupric carboxylate **B**. Subsequently, addition of phosphorus radical **A** at the α-position of the triple bond of **B** gives intermediate **C**, where the hydroxyl radical abstracts a hydrogen atom from **C** to form intermediate **D**. Intermediate **D** loses CO₂ to form intermediate **E**, which is then reduced by [H] to form intermediate **F**. Finally, **F** is converted to the product **3a**.



Scheme 4 Proposed reaction mechanism.



which is ultimately trapped by the hydroxyl radical to form intermediate **D**. Then **D** releases one molecular CO₂ to produce alkenyl copper intermediate **E**. Finally, the protonolysis of the intermediate leads 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 Csp³–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 an inexpensive CuSO₄·5H₂O catalyst, using readily available alkynyl acids only producing CO₂ means that this facile protocol will be attractive for academia and industry.

We acknowledge financial support from the Chinese National Natural Science Foundation (21173178, 21232005, and 21375113), GD2012-D01-001, the National Basic Research Program of China (2012CB821600), and the Program for Changjiang Scholars and Innovative Research Team in University.

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