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# Copper-Catalyzed Synthesis of Alkylphosphonates from *H*-Phosphonates and *N*-Tosylhydrazones

Wenjun Miao,<sup>a</sup> Yuzhen Gao,<sup>a</sup> Xueqin Li,<sup>a</sup> Yuxing Gao,<sup>a</sup> Guo Tang,<sup>a,\*</sup> and Yufen Zhao<sup>a,b</sup>

<sup>a</sup> Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, People's Republic of China

Fax: (+86)-592-218-5780; e-mail: t12g21@xmu.edu.cn

<sup>b</sup> Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, People's Republic of China

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**Abstract:** A new catalytic system for the alkylation of *H*-phosphonates and diphenylphosphine oxide with *N*-tosylhydrazones has been developed. In the presence of copper(I) iodide and base, *H*-phosphonates react with *N*-tosylhydrazones to afford the corresponding coupled alkylphosphonates in good to excellent yields without any ligands. Alkylphosphonates can also be prepared in a one-pot process directly from carbonyl compounds without the isolation of tosylhydrazone intermediates.

**Keywords:** alkylphosphonates; carbonyl compounds; copper catalysis; *H*-phosphonates; *N*-tosylhydrazones

Organic phosphonates have all along attracted considerable attention as they are significant compounds in organic synthesis,<sup>[1]</sup> flame retardants,<sup>[2]</sup> and biological chemistry.<sup>[3]</sup> In synthetic organic chemistry, alkylphosphonates are crucial intermediates which have been widely utilized as prominent precursors for the synthesis of various materials,<sup>[4]</sup> as well as direct precursors of olefins through the Horner–Wadsworth–Emmons reaction.<sup>[5]</sup> The most traditional methods for the formation the P–C(*sp*<sup>3</sup>) bond are the Michaelis–Arbuzov<sup>[6]</sup> and Michaelis–Becker reactions.<sup>[7]</sup> Although prevalent in scope, the trivalent phosphorus compounds used in the Michaelis–Arbuzov reaction are usually low in stability and emit a foul odor. The Michaelis–Becker reaction sometimes requires a strong base and long reaction times, and these drawbacks can limit the range of substrates and the yield of products. The demand for functionalized organic phosphonates has stimulated extensive studies on

phosphorylation<sup>[8]</sup> and P–C(*sp*<sup>3</sup>) bond-forming reactions involving arylmethyl halides/alcohols/carboxylic acids catalyzed by Pd,<sup>[9a,b]</sup> Lewis acids,<sup>[9c,d]</sup> Cu<sup>[9e]</sup> and N<sub>2</sub>H<sub>4</sub>.<sup>[9f]</sup>

On the other hand, it is noteworthy that sulfonyl hydrazones are versatile synthetic intermediates<sup>[10]</sup> that have triggered the interest of numerous researchers recently. From 2007, Barluenga<sup>[11]</sup> and Wang's group<sup>[12]</sup> had developed a series of transformations with tosylhydrazones. Sulfonyl hydrazones are employed as a secure and convenient source of diazo compounds from carbonyl compounds in a variety of new transformations. To the best of our knowledge, as early as 1981, Bertz<sup>[13]</sup> had reported that refluxing trisylhydrazones with diphenylphosphine oxide in THF for several days resulted in aromatic organophosphorus compounds in 23–90% yields. Inokawa<sup>[14]</sup> and Yamashita's group reported that dimethyl 1-(*N'*-tosylhydrazino)-alkanephosphonates reacted with sodium tetrahydridoborate to furnish alkyl phosphonates.<sup>[15]</sup> However, the dehydrazination reaction competed with the β-elimination reaction often resulting in low yields. Since copper has been identified as a useful catalyst for cross-coupling reactions involving carbon–carbon bonds and carbon–heteroatom bonds,<sup>[16]</sup> it was suggested that it might provide an efficient approach for the alkylation of phosphonates using carbonyl compounds and *H*-phosphonates/diphenylphosphine oxide as coupling partners.

This copper-catalyzed alkylphosphonation depends greatly on the reaction conditions. To optimize the conditions, we examined the effect of solvent, base, and ligand on the reaction yield (Table 1). *N*-Tosylhydrazone (**1a**) and diethyl *H*-phosphonate (**2a**) were used as the substrates in these studies. The yield of **3a** was determined based on the <sup>31</sup>P NMR signal-integration method. When a mixture of **1a** (0.60 mmol) and

**Table 1.** Optimization of reaction conditions.<sup>[a]</sup>

$  \begin{array}{c} \text{Ph} \\ \parallel \\ \text{C}=\text{N}-\text{NH}-\text{Ts} \\ \text{1a} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{H}-\text{P}-\text{OEt} \\ \text{2a} \end{array} \xrightarrow[\text{solvent, } T [^\circ\text{C}], 2 \text{ h}]{\text{catalyst, base, ligand [10\%]}} \begin{array}{c} \text{O} \\ \parallel \\ \text{Ph}-\text{CH}_2-\text{P}-\text{OEt} \\ \text{3a} \end{array}  $						
Entry	Catalyst	Ligand	Base	Solvent	<i>T</i> [°C]	Yield [%]
1	CuI	–	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	70	77
2	CuI	–	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	70	75
3	CuI	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	70	80
4	CuI	BPy	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	80	79
5	CuI	BPy	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	82
6	CuI	PHEN	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	88
7	CuI	TMEDA	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	75
8	<b>CuI</b>	–	<b>Cs<sub>2</sub>CO<sub>3</sub></b>	<b>DME</b>	<b>80</b>	<b>96</b>
9	CuI	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	50	50
10	CuI	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	100	85
11	–	–	–	DME	80	0
12	–	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	5
13	CuI	–	–	DME	80	0
14	CuI	–	<i>t</i> -BuOK	DME	80	93
15	CuI	–	K <sub>3</sub> PO <sub>4</sub>	DME	80	78
16	CuI	–	Et <sub>3</sub> N	DME	80	10
17	CuI	–	DBU	DME	80	0
18	CuCl	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	92
19	CuBr	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	65
20	Cu <sub>2</sub> O	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	43
21	CuCl <sub>2</sub>	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	90
22	Cu(OTf) <sub>2</sub>	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	89
23 <sup>[b]</sup>	–	–	–	DME	80	16
24 <sup>[b]</sup>	–	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	0
25 <sup>[b]</sup>	CuI	–	–	DME	80	28
26 <sup>[b]</sup>	CuI	–	Cs <sub>2</sub> CO <sub>3</sub>	DME	80	82

<sup>[a]</sup> Reaction conditions: **1a** (0.60 mmol), **2a** (0.50 mmol), copper salt (0.050 mmol), base (0.75 mmol), solvent (2.5 mL), and N<sub>2</sub> for 2 h in a sealed tube. Yields were determined by <sup>31</sup>P NMR.

<sup>[b]</sup> Diphenylphosphine oxide (**2f**) (0.50 mmol) was used.

**2a** (0.50 mmol, <sup>31</sup>P NMR: δ = 7.0 ppm) was heated in the presence of CuI (0.050 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (0.75 mmol) at 80 °C under nitrogen for 2 h, diethyl benzylphosphonate (**3a**, <sup>31</sup>P NMR: δ = 26.4 ppm) was obtained in excellent yield (entry 8). The structure of **3a** was confirmed by its <sup>1</sup>H and <sup>13</sup>C NMR spectra and mass spectrometry. Under similar reaction conditions, the addition of nitrogen ligands such as bipyridine, 1,10-phenanthroline monohydrate and *N,N,N',N'*-tetramethylethylenediamine resulted in 75–88% product yields (Table 1, entries 4–7). CuCl, CuBr, Cu<sub>2</sub>O, CuCl<sub>2</sub> and Cu(OTf)<sub>2</sub> were less effective for the alkylation of *H*-phosphonate (entries 18–22).

In the control reactions, **1a** and diethyl *H*-phosphonate without CuI were heated at 80 °C for 2 h under nitrogen atmosphere, to afford **3a** in only 0–5% yields (entries 11 and 12). This result indicates that a catalyst is essential to achieve a high yield of product **3a**. The choice of solvent is also vital to the catalytic reaction

(entries 1–8). The best solvent was 1,2-dimethoxyethane (entry 8). In the absence of a base, the catalytic reaction did not proceed. Various bases were tested for the catalytic reaction. Among them, Cs<sub>2</sub>CO<sub>3</sub> gave the highest yield of product **3a**. Others such as K<sub>3</sub>PO<sub>4</sub>, triethylamine and DBU were less effective, giving **3a** in very low yield (entries 15–17). Some strong bases, *t*-BuOK, also gave satisfactory yields (entry 14). The choice of temperature is also very crucial for the present catalytic reaction (entries 1–10). The catalytic reaction proceeded slowly at 50–70 °C (entries 1, 2, and 9). However, when the temperature was raised to 80 °C, the alkylation of *H*-phosphonate could be carried out in 1,2-dimethoxyethane and the reaction gave **3a** in 96% yield. When the temperature was raised to 100 °C, the yield of product **3a** decreased greatly (entry 10).

The control experiments had also been made on diphenylphosphine oxide (**2f**) to prove that the reaction is truly catalytic. When a mixture of **1a** (0.60 mmol) and **2f** (0.50 mmol, <sup>31</sup>P NMR: δ = 19.0 ppm) was heated in the presence of CuI (0.050 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (0.75 mmol) at 80 °C under nitrogen for 12 h, benzyl diphenylphosphine oxide (**3x**, <sup>31</sup>P NMR: δ = 29.5 ppm) was obtained in 82% yield (entry 26). Without CuI, **3x** was obtained in only 0–16% yields (entries 23 and 24).

Under the optimized conditions shown in footnote [a] of Table 1, we next examined the reactions of various substituted *N*-tosylhydrazones with *H*-phosphonates to probe the scope of the reaction (Table 2). It was found that a wide range of *N*-tosylhydrazones derived from aldehydes and ketones proceeded efficiently. Various benzaldehydes with electron-donating substituents were investigated; the corresponding products were obtained in high yields (**3b–3d**). In addition, this reaction is also compatible with halogen substituents on the aromatic ring of benzaldehydes **1**. Thus 4-fluoro-, 4-chloro-, and 4-bromobenzaldehyde tosylhydrazones reacted with **2a** to give products **3e–3g** in 92%, 82% and 86% yields, respectively. Although electron-withdrawing substrates suffered from poor reactivity, it was notable that addition of 50% equiv. CuI to the reaction system and simultaneously increasing the reaction time to 12 h led to the formation of products **3m** and **3n** in 86 and 82% yields. 2-Furaldehyde tosylhydrazone and 2-thiophenecarboxaldehyde tosylhydrazone also reacted smoothly with *H*-phosphonate to afford products **3k** and **3l**, respectively, in 82% and 90% yields. The present catalytic reaction was also successfully applied to aliphatic substrates in satisfactory yields. Thus, the tosylhydrazones of phenylacetaldehyde, phenylpropyl aldehyde and isobutyraldehyde reacted with diethyl *H*-phosphonate to afford the corresponding alkyl phosphonation products **3t**, **3u** and **3v** in 78, 81 and 75% yields, respectively. In regard to the *H*-phospho-

**Table 2.** Copper-catalyzed coupling of *H*-phosphonate with *N*-tosylhydrazones.<sup>[a]</sup>

$\begin{array}{c} \text{R}^1 \\   \\ \text{R}^2 - \text{C} = \text{NNHTs} \\ \mathbf{1} \end{array} + \begin{array}{c} \text{O} \\    \\ \text{H} - \text{P} - \text{R}^3 \\   \\ \text{R}^4 \\ \mathbf{2} \end{array} \xrightarrow[\text{DME, 80 } ^\circ\text{C}]{\text{CuI, Cs}_2\text{CO}_3} \begin{array}{c} \text{R}^1 \\   \\ \text{R}^2 - \text{C} - \text{P}(\text{R}^3)(\text{R}^4) \\ \mathbf{3a-j-3z} \end{array}$	
$\mathbf{2a}$ : $\text{R}^3, \text{R}^4 = \text{EtO}$ , $\mathbf{2c}$ : $\text{R}^3, \text{R}^4 = i\text{-PrO}$ , $\mathbf{2e}$ : $\text{R}^3 = \text{Ph}$ , $\text{R}^4 = \text{EtO}$ , $\mathbf{2b}$ : $\text{R}^3, \text{R}^4 = \text{MeO}$ , $\mathbf{2d}$ : $\text{R}^3, \text{R}^4 = n\text{-BuO}$ , $\mathbf{2f}$ : $\text{R}^3, \text{R}^4 = \text{Ph}$	

<sup>[a]</sup> Reaction conditions: **1** (1.10 mmol), **2** (1.0 mmol), CuI (0.10 mmol), Cs<sub>2</sub>CO<sub>3</sub> (1.50 mmol), solvent (2.5 mL), 2 h, 80 °C, under N<sub>2</sub>. Isolated yield.

<sup>[b]</sup> CuI (0.50 mmol), 12 h needed.

<sup>[c]</sup> 12 h needed.

nates, in addition to **2a**, dimethyl (**2b**), diisopropyl (**2c**), and dibutyl *H*-phosphonates (**2d**) all could be used as the substrates, generating the corresponding alkylphosphonates (**3o–3q**) in 50–77% yields. When ethyl phenylphosphinate (**2e**) was used, **3r** was obtained in high yield. Cyclohexanone and acetone tosylhydrazones were also examined. Unfortunately, only trace amounts of the desired P–C(*sp*<sup>3</sup>) bond-forming products were detected by <sup>31</sup>P NMR.

It is worth noting that the copper-catalyzed alkyl phosphonation reaction can be also applied in the preparation of alkyldiphenylphosphine oxides in 75–92% yields (Table 2, **3w–3z**). This method should be a good addition to the previous P–C(*sp*<sup>3</sup>) bond formation methods.<sup>[17]</sup>

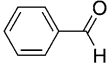
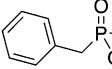
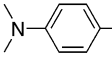
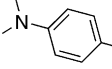
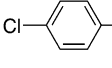
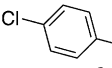
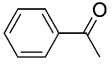
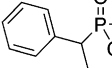
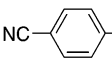
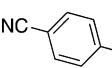
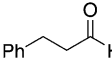
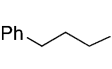
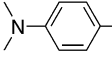
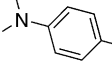
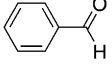
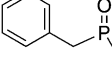
As tosylhydrazones could be easily prepared by simply mixing sulfonyl hydrazides and the carbonyl compounds, we investigated whether the reaction could be carried out in one-pot directly from carbonyl compounds without the isolation of tosylhydrazone intermediates. We were glad to achieve positive results. After stirring the carbonyl compound and *p*-tosylhydrazine for 1 h at room temperature, we added Cs<sub>2</sub>CO<sub>3</sub> and CuI, and then the mixture was heated at 80 °C for another 2 h. The products were isolated with a slight decrease in the yields (Table 3)

With the synthetic alkylphosphonates in hand, we next prepared two olefins (**5a** and **5b**) in good yields from aldehydes and alkylphosphonates, employing a Horner–Wadsworth–Emmons (HWE) reaction (Scheme 1).

Although the detailed mechanism remains ambiguous at present, a possible mechanism for this copper-catalyzed alkyl phosphonation of *N*-tosylhydrazones with *H*-phosphonates is described as follows: (i) the thermolysis of *N*-tosylhydrazone under basic conditions *in situ* generates a diazo compound, which subsequently releases nitrogen and leads to a Cu-carbene complex; (ii) subsequently a copper-associated ylide is formed by attack of the lone-pair electrons of the P(III) phosphite atom on the electron-deficient copper carbene; (iii) the final product was then formed by catalyst dissociation.<sup>[18]</sup> Unfortunately, no intermediate has been captured; the details of the mechanism will be the subject of future studies.

In conclusion, we have developed a novel copper-catalyzed phosphorus-carbon (*sp*<sup>3</sup>) bond-forming reaction which proceeds in good yields and does not require any ligand. The reactions described provide a novel access to alkylphosphonates as well as alkyldiphenylphosphine oxides and cover a broad scope of substrates. Moreover, the *N*-tosylhydrazones used are readily available from carbonyl compounds. Alkylphosphonates can be prepared in a one-pot directly from carbonyl compounds without the isolation of tosylhydrazone intermediates. Therefore, this protocol will have wide application for the construction of bio-

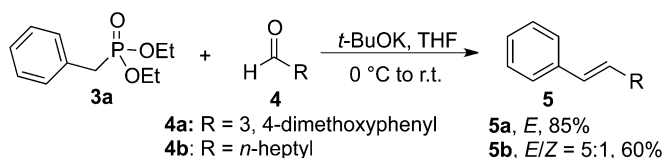
**Table 3.** Preparation of alkylphosphonates from *H*-phosphonates and carbonyl compounds in a one-pot process.<sup>[a]</sup>

$\text{R}^1-\text{C}(=\text{O})-\text{R}^2 \xrightarrow[2) \text{H}-\text{P}(\text{O})(\text{R}^3)(\text{R}^4), \text{CuI}, \text{Cs}_2\text{CO}_3, 80^\circ\text{C}, 2 \text{ h}]{1) \text{TsNHNH}_2, \text{DME}, \text{r.t.}, 1 \text{ h}}$		$\text{R}^1-\text{C}(\text{R}^2)-\text{P}(\text{O})(\text{R}^3)(\text{R}^4)-\text{OEt}$	
Entry	Carbonyl Compound <b>2</b>	Product <b>3</b>	Yield [%]
1	 <b>2a</b>	 <b>3a</b>	75
2	 <b>2a</b>	 <b>3d</b>	80
3	 <b>2a</b>	 <b>3f</b>	73
4	 <b>2a</b>	 <b>3h</b>	77
5 <sup>[b]</sup>	 <b>2a</b>	 <b>3m</b>	70
6 <sup>[c]</sup>	 <b>2a</b>	 <b>3r</b>	78
7 <sup>[c]</sup>	 <b>2e</b>	 <b>3de</b>	68
8 <sup>[c]</sup>	 <b>2f</b>	 <b>3f</b>	60

<sup>[a]</sup> *Reaction conditions:* (i) carbonyl compound (1.10 mmol), TsNHNH<sub>2</sub> (1.10 mmol), DME (2.0 mL), 1 h, room temperature; (ii) CuI (0.10 mmol), **2** (1.0 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.50 mmol), 80 °C, 2 h, under N<sub>2</sub>. Isolated yield.

<sup>[b]</sup> CuI (0.50 mmol), 80 °C, 12 h needed.

<sup>[c]</sup> 80 °C, 12 h needed.

**Scheme 1.** The synthesis of olefins using the HWE reaction.

logically active molecules, catalytic ligands and organophosphorus compounds.

## Experimental Section

### Typical Procedure for the Synthesis of *N*-Tosylhydrazones

A solution of pure TsNHNH<sub>2</sub> (5.0 mmol) in methanol (5.0 mL) was stirred and heated to 60 °C until the TsNHNH<sub>2</sub> was completely dissolved. The mixture was cooled to room temperature, and then carbonyl compounds (5.0 mmol) were dropped into the mixture slowly. After approximately 30 min the mixture was cooled to 0 °C and the product removed by filtration, washed with petroleum ether then evaporated under vacuum to afford the pure products. The

reaction provides the *N*-tosylhydrazones in about 80% yields. Because of the relatively low activity of diphenyl ketone, the reaction at room temperature may be incomplete. It should be reacted in refluxing methanol for approximately 1 h. The reaction could be monitored through TLC.

### General Procedure for the Coupling of *H*-Phosphonates with *N*-Tosylhydrazones

An oven-dried Schlenk tube containing CuI (19.0 mg, 0.10 mmol), *N*-tosylhydrazones (1.10 mmol), Cs<sub>2</sub>CO<sub>3</sub> (489 mg, 1.50 mmol) was evacuated and purged with nitrogen three times. Freshly distilled DME (2.5 mL) and diethyl *H*-phosphonate (**2a**) (1.0 mmol) were sequentially added to the system at room temperature. The reaction mixture was heated with stirring at 80 °C for 2 h. The reaction mixture was allowed to cool to ambient temperature, and then transferred to a round-bottom flask. Silica gel (3.0 g) was added, and the solvent was removed under reduced pressure to afford a free-flowing powder. This powder was then dry-loaded onto a silica gel column and purified by flash chromatography using petroleum ether:AcOEt (2:1, v/v) as the eluent to give diethyl benzylphosphonate (**3a**). A number of products were synthesized according to this procedure (**3a–3l**), other phosphonates were prepared similarly.



### Preparation of Alkylphosphonates from *H*-Phosphonates and Carbonyl Compounds in One Pot

In a Schlenk tube a mixture of TsNHNH<sub>2</sub> (1.10 mmol) in DME (2.0 mL) was stirred and heated to 60 °C until the TsNHNH<sub>2</sub> was dissolved as much as possible. The mixture was cooled to room temperature, and then the carbonyl compound (1.10 mmol) dissolved in DME (1.0 mL) was dropped into the mixture slowly. After approximately 1 h CuI (19.0 mg, 0.10 mmol), diethyl *H*-phosphonate (**2a**) (1.0 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (489 mg, 1.50 mmol) were sequentially added to the system at room temperature. The reaction mixture was heated with stirring at 80 °C for 2 h. When the reaction was complete, the crude mixture was allowed to reach room temperature, and then transferred to a round-bottom flask. Silica gel (3.0 g) was added, and the solvent was removed under reduced pressure to afford a free-flowing powder. This powder was then dry-loaded onto a silica gel column and purified by flash chromatography using petroleum ether:AcOEt (2:1, v/v) as the eluent.

### Synthesis of Olefins from Diethyl Benzylphosphonate using the HWE Reaction

A mixture of aldehyde **4** (1.0 mmol) and diethyl benzylphosphonate **3a** (228 mg, 1.0 mmol) in anhydrous THF (5.0 mL) was slowly added to a dry THF solution of *t*-BuOK (135 mg, 1.2 mmol) at 0 °C under argon. After the reaction mixture had been stirred at 0 °C for 1 h, the mixture was allowed to warm up to room temperature and stirred for another 2 h. Then the solvent was removed under reduced pressure. The crude product was purified by column chromatography using petroleum ether:AcOEt (10:1, v/v) as the eluent to afford compound **5**.

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