

## Reactions of Acyl Tributylphosphonium Chlorides and Dialkyl Acylphosphonates with Grignard and Organolithium Reagents

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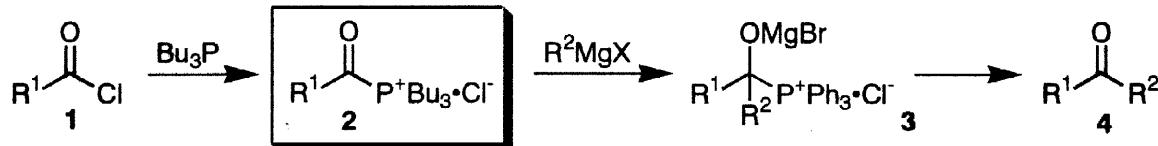
**Abstract:** Ketones and esters (**4**) were effectively prepared by reaction of Grignard reagents with acyl tributylphosphonium chlorides (**2**), diethyl acylphosphonates (**5**), or diisopropyl acylphosphonate (**6**) derived from acid chlorides and chloroformates (**1**). Although by the method with **2**, **4** is prepared in one-pot operation from **1** and generally in a higher yield, the method with **5** or **6** proved to compensate for the synthesis of **4** with **2** in some respects. The reactivities of **2**, **5**, and **6** as electrophiles were also evaluated by comparing their reduction potentials with those of acid chlorides.

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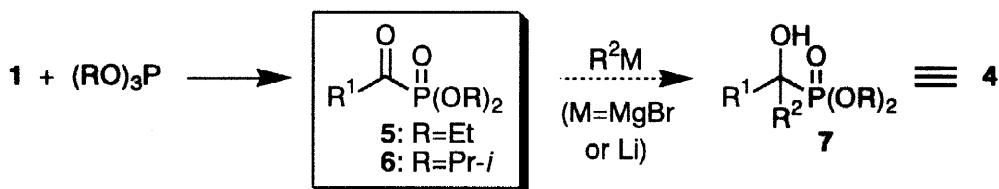
### Introduction

Recently, we found that the reactions of Grignard reagents with acyl tributylphosphonium salts (**2**) *in situ* generated from acid chlorides (**1**) and  $Bu_3P$  in THF at  $-22^\circ C$  provide a convenient and simple access to ketones (**4**) (Scheme 1).<sup>1</sup> Although it was demonstrated that various types of **4** are prepared in excellent yields by this method, there appears to be some room for improvement as follows: (i) the ketone synthesis is spoiled by formation of tertiary alcohols without carefully controlled addition of one equivalent of  $R^2MgBr$  to **1**; (ii) iso- $PrMgBr$  works as a hydride-donor reagent against **2** as well as a carbon nucleophile, resulting in much lower yields of **4**; (iii) the ketone synthesis with  $PhMgBr$  and **2** derived from  $R'CH_2COCl$  ( $R' \neq H$ ) is unsuccessful,<sup>2</sup> where deprotonation of **2** by  $PhMgBr$  seems to precede its nucleophilic addition to **2**.

In order to establish a more general method for synthesis of **4** from **1** via **2** or its analogs, we turned our attention to reactions of Grignard and organolithium reagents with dialkyl acylphosphonates **5** and **6** (Scheme 2) as well as those with **2**. As a promising alternative to **2**, phosphonates **5** and **6** were chosen for the



Scheme 1



Scheme 2

following reasons: (i) they are easily prepared via a Michaelis-Arbuzov reaction with **1** and  $(RO)_3P$  ( $R=Et$  or iso- $Pr$ );<sup>3</sup> (ii)  $\alpha$ -hydroxyalkylphosphonates (**7**) are regarded as carbonyl equivalents,<sup>4,5</sup> similarly to  $\alpha$ -hydroxyalkyl tributylphosphonium salts;<sup>6</sup> (iii) reactions of **5** and **6** with Grignard and organolithium reagents have never been studied as far as we are aware, although acyl phosphonates and phosphonamides such as **5** have proved to serve as acylating reagents for alcohols,<sup>3a,7,8</sup> amines,<sup>9</sup> and enolates.<sup>10</sup> In this paper, we describe that **5** and **6** are useful alternatives to **2** in the preparation of **4**, although the method with the phosphonates requires an additional step to transform the initial product such as **7** to **4**.

## Results and Discussion

Table 1 summarizes the results of the reactions of **2** with Grignard and organolithium reagents. As previously reported,<sup>1</sup> **2** was prepared by addition of  $Bu_3P$  to a THF solution of **1** at  $-22^\circ C$ , and the THF solution was subjected to reactions with Grignard reagents (1.0 eq. to **1**) at the same temperature. When **2** derived from benzoyl or acetyl chloride was treated with  $PhMgBr$  or  $MeMgBr$ , **4** was formed in an excellent yield without any formation of a tertiary alcohol **8** (runs 1~3). However, when organolithium reagents were utilized instead of Grignard reagents, the transformation of **2** into **8** prevailed over the formation of **4** (runs 1~3). These results imply that a lithiated counterpart of **3** (cf. Scheme 1) decomposes into **4** substantially faster than **3**, leading to the overaddition of organolithium reagents affording **8** as the main product.

The *in situ* conversion of chloroformates into **2** followed by reaction with Grignard reagents gave the corresponding esters in excellent yields (runs 4 and 5). Without pretreatment with  $Bu_3P$ , ethyl chloroformate

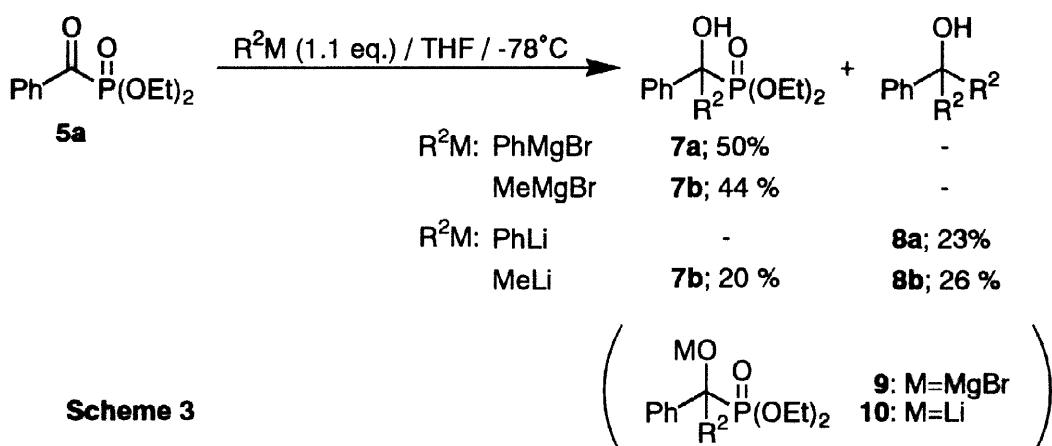
Table 1

Run	Substrate		$R^2$	Products (%) <sup>a)</sup>		
	$R^1$	$R^1$		$R^2MgBr$	$R^2Li$	
1	<b>2a</b>	Ph	Ph	<b>4a</b> (93)	<b>4a</b> (8)	<b>8a</b> (27)
2	<b>2a</b>	Ph	Me	<b>4b</b> (98) <sup>b,c)</sup>	<b>4b</b> (10) <sup>b)</sup>	<b>8b</b> (33) <sup>b)</sup>
3	<b>2b</b>	Me	Ph	<b>4b</b> (84) <sup>b)</sup>	<b>4b</b> (trace)	<b>8c</b> (19)
4	<b>2f</b>	EtO	Ph	<b>4f</b> (98) <sup>b)</sup>	<b>4f</b> (trace)	<b>8a</b> (19)
5	<b>2g</b>	PhO	Me	<b>4g</b> (75) <sup>b)</sup>		<b>4g</b> (4) <sup>b)</sup>

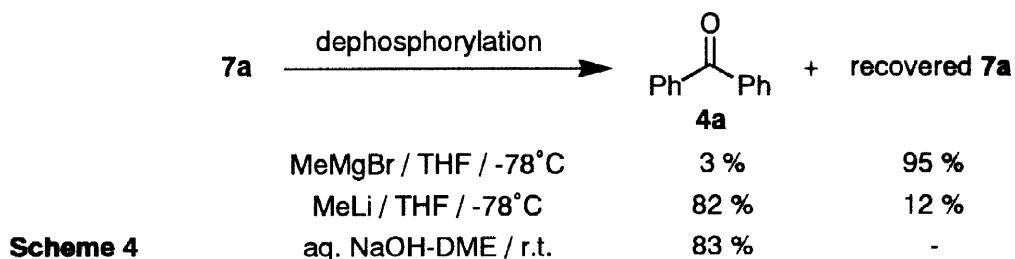
a) Isolated yield; b) Determined by GLC; c) From our previous work.<sup>1</sup>

reacted with  $\text{PhMgBr}$  under essentially the same conditions to give  $\text{PhCO}_2\text{Et}$ , but only in 28% yield. Thus, preformation of **2** provides a simple solution to the problems associated with preparation of carbonyl compounds by reactions of Grignard reagents not only with acid chlorides but also with chloroformates. Preparation of esters from chloroformates via **2** was unsuccessful (runs 4 and 5), when  $\text{PhLi}$  or  $\text{MeLi}$  was employed instead of Grignard reagents, as in the case with **2** generated from acid chlorides.

In order to evaluate the possibility of the reactions of **5** and **6** with Grignard or organolithium reagents as a novel access to **4**, **5a** was used as a model compound (Scheme 3). The phosphonate was prepared in 90% yield via a Michaelis-Arbuzov reaction of benzoyl chloride and  $(\text{EtO})_3\text{P}$ . The reactions were carried out by addition of the organometallic reagents (1.1 eq. to **5a**) to a THF solution of **5a** at  $-78^\circ\text{C}$ . As shown in Scheme 3,  $\text{PhMgBr}$  and  $\text{MeMgBr}$  reacted with **5a** to give not **4** but  $\alpha$ -hydroxyphosphonates **7a** and **7b**, respectively, in moderate yields. In the reactions of  $\text{PhLi}$  and  $\text{MeLi}$  with **5a**, the formation of tertiary alcohols **8a** and **8b** were preferred to that of **7**.



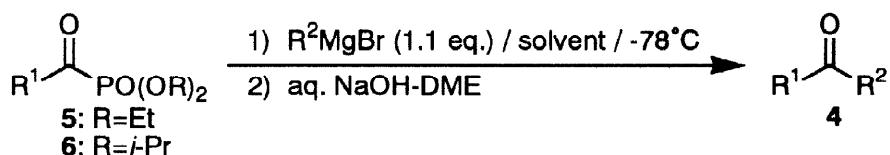
It was reported that  $\alpha$ -hydroxyphosphonates such as **7**,<sup>4,5</sup>  $\alpha$ -silyloxyphosphonates,<sup>6</sup> and  $\alpha$ -silyloxyphosphonamides<sup>7</sup> are regarded as protected forms of carbonyl groups, of which deprotection is realized under basic conditions or with a fluoride ion. Similarly, the adducts **9** and **10** (Scheme 3) can be considered as protected ketones, and no formation of tertiary alcohols in the reactions with Grignard reagents can be attributed to the fact that **10** is much more unstable than **9** and decomposes into **4** under the reaction conditions, as confirmed by the following experiments (Scheme 4). On treatment with  $\text{MeMgBr}$ , **7a** stayed almost intact, to be recovered in 95% yield, and only trace amounts of **4a** were obtained. In contrast,  $\text{MeLi}$



effectively promoted the dephosphorylation of **7a**, affording **4a** in 82% yield. In the reaction of **5** with  $R^2Li$ , **4** is formed *in situ* via **10** and further transformed to a tertiary alcohol by overaddition of the organolithium reagent.

Based on previous reports,<sup>4,5</sup> dephosphorylation of **7a** was also attempted under aqueous basic conditions. Treatment with 1.0 eq. of NaOH in H<sub>2</sub>O-DME at room temperature proved to be effective for the transformation of **7a** to **4a** (Scheme 4). Accordingly, coupling of **5** with Grignard reagents followed by dephosphorylation of the crude product in aq. NaOH-DME was expected to provide a more feasible access to **4** without isolation of the intermediates **7**. By this reaction sequence, **4a** was obtained in 55% yield from **5a** (Table 2, run 1), which is a much better yield than that (42%) obtained by the procedure which includes the isolation of **7a**. Preparation of **4a** was also conducted by employing DME or toluene as a solvent instead of THF. Although DME exhibited no effect on the transformation, employing toluene as a solvent increased the yield of **4a** remarkably (runs 2 and 3). Thus, we have prepared various **4** by addition of Grignard reagents to a toluene solution of **5** followed by dephosphorylation in aq. NaOH-DME. The results are also included in Table 2. All of **5** examined here were obtained in 91~71% yields by Michaelis-Arbuzov reactions similarly to the case of **5a**. As shown in runs 4 and 7~11, various **5** smoothly entered the reaction course with PhMgBr or MeMgBr, affording **4** in good yields. However, a function of iso-PrMgBr as a hydride-donor reagent predominated over that as a nucleophile even in the reaction with **5a**, resulting in the formation of the desired ketone in a poor yield (run 6).

It is noteworthy that the method with **5** compensates for the ketone synthesis with **2** in the following respects. Acyl phosphonium salts **2c~2e**, generated from Bu<sub>3</sub>P with EtCOCl, CH<sub>3</sub>(CH<sub>2</sub>)<sub>8</sub>COCl, or PhCH<sub>2</sub>CH<sub>2</sub>COCl, reacted with PhMgBr to give the corresponding ketones in low yields: 10, 5,<sup>1</sup> and 7%,<sup>1</sup> respectively.<sup>2</sup> These poor results appear to arise from the conversion of the acyl phosphonium salts **2** to their

**Table 2**

Run	Substrate R <sup>1</sup>	R <sup>2</sup>	Solvent	Yield of 4 (%)	Run	Substrate R <sup>1</sup>	R <sup>2</sup>	Solvent	Yield of 4 (%)		
1	<b>5a</b>	Ph	Me	THF	55 <sup>a)</sup>	9	<b>5d</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub>	Ph	toluene	75 <sup>b)</sup>
2	"	"	"	DME	50 <sup>a)</sup>	10	<b>5e</b>	PhCH <sub>2</sub> CH <sub>2</sub>	"	"	73 <sup>b)</sup>
3	"	"	"	toluene	72 <sup>a)</sup>	11	<b>5f</b>	EtO	"	"	71 <sup>a,d)</sup>
4	"	"	Ph	"	81 <sup>b)</sup>	12	<b>6a</b>	Ph	Me	"	75 <sup>a)</sup>
5 <sup>c)</sup>	"	"	"	"	81 <sup>b)</sup>	13	"	"	Ph	"	76 <sup>b)</sup>
6	"	"	i-Pr	"	12 <sup>a)</sup>	14	<b>6b</b>	Me	"	"	66 <sup>a)</sup>
7	<b>5b</b>	Me	Ph	"	70 <sup>a)</sup>	15	<b>6c</b>	Et	"	"	73 <sup>a)</sup>
8	<b>5c</b>	Et	"	"	70 <sup>a)</sup>						

a) Determined by GLC. b) Isolated yield. c) Two equivalents of PhMgBr was used.

d) The reaction with the Grignard reagent was carried out at -22°C, and dephosphorylation was performed by treatment with a solution of NaOH in EtOH.

enolates as described previously.<sup>1</sup> Furthermore, the ketone synthesis by the method with **2** is spoiled by formation of tertiary alcohols without carefully controlled addition of one equivalent of Grignard reagents to **2**. For example, in the reaction of the phosphonium salt **2a** generated from benzoyl chloride, addition of PhMgBr in 2 eq. amounts resulted in the formation of the tertiary alcohol **8a** in 13% yield as a by-product. On the other hand, **5** derived from R'CH<sub>2</sub>COCl (R'≠H) smoothly entered the reaction with PhMgBr, giving **4** without any competition with deprotonation process at  $\alpha$ -methylene by the Grignard reagent (runs 8–10). Use of an excess amount of PhMgBr did not affect the reaction of **5a**. When **5a** was treated with 2 eq. of PhMgBr, **4a** was obtained in 81% yield without any formation of a tertiary alcohol, similarly to the case with 1.1 eq. of the reagent (runs 4 and 5). This result indicates that the ketone synthesis with **5** does not require stringent experimental conditions such as controlled addition of one equivalent of Grignard reagents at all, as in the acylation of organometallic reagents with N-methoxy-N-methylamides (Weinreb amides).<sup>11,12</sup> Thus, utilizing **5** as an acylating reagent proves to overcome problems (i) and (iii) encountered in the ketone synthesis with **2** and Grignard reagents.

The coupling of **6**, similarly prepared from the corresponding acid chlorides and (iso-PrO)<sub>3</sub>P in 72–32% yields, with Grignard reagents proceeded smoothly in a manner similar to the case with **5** (runs 12–15). However, the acylation of Grignard reagents through the reactions with **5** provides a more effective access to ketones because the formation of **6** by Michaelis-Arbuzov reactions takes place in a lower yield than that of **5**.

Cathodic reduction potentials have been used to measure the electrophilicity of an organic compounds.<sup>25</sup> In order to obtain cathodic reduction potentials and evaluate their reactivities as electrophiles, cyclic voltammetry was performed for acid chlorides (**1**), acyl phosphonium salts **2**, and acylphosphonates **5** and **6**. The results are summarized in Table 3. Although benzoyl chloride (**1a**) exhibited a cathodic wave at -1.56 V, cathodic reduction of **1b**–**1f** requires remarkably negative potentials (< -2.6 V). Treatment of **1** with Bu<sub>3</sub>P significantly shifted the cathodic peak towards a positive direction. The observed potential shifts amounted to more than 1.0 V for **1b**–**1f**, indicating that **2** formed *in situ* is a much better electron acceptor than **1**. Although the reduction potential of **5a** was essentially the same as that of **1a**, **5b**–**5f** exhibited cathodic peaks at potentials as positive as 0.6 V in comparison to **1b**–**1f**. The cathodic waves for **6a**–**6c** were observed at similar potentials to those for **5a**–**5c**. It is worth noting that **5a** and **6a** exhibit anodic waves at -

**Table 3** Reduction Potentials of **1**, **2**, and **5**<sup>a</sup>

R <sup>1</sup> in		Reduction Potential (V vs. SCE)			
		X=Cl ( <b>1</b> )	X=P <sup>+</sup> Bu <sub>3</sub> ( <b>2</b> )	X=PO(OEt) <sub>2</sub> ( <b>5</b> )	X=PO(OPr-iso) <sub>2</sub> ( <b>6</b> )
<b>a</b>	Ph	-1.56	-1.10	-1.56	-1.60
<b>b</b>	Me	-2.67	-1.46	-1.95	-2.02
<b>c</b>	Et	-2.67	-1.48	-2.03	-2.06
<b>d</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub>	-2.60	-1.50	-1.98	
<b>e</b>	PhCH <sub>2</sub> CH <sub>2</sub>	-2.61	-1.42	-1.96	
<b>f</b>	EtO	-2.87	-1.87	-2.54	

a) Obtained by cyclic voltammetry of the acyl compound (5 mM) in CH<sub>3</sub>CN (0.1 M Bu<sub>4</sub>NClO<sub>4</sub>) at a glassy carbon electrode.

1.47 V and -1.52 V on the reverse scan, respectively, although only cathodic responses were observed on the voltammograms of other acyl compounds including **1**. This quasi-reversible electrochemical behavior implies that ketyl anion radicals generated through one-electron reduction of C=O bonds will be stabilized by the introduction of phosphonate groups. Comparing the cathodic reduction potentials of these acyl compounds suggests that electrophilic reactivity follows the order **2** > **5**, **6** > **1**, which is reflected in the results of their reactions with Grignard reagents.<sup>26</sup> Thus, introduction of the tetra- and penta-valent phosphorus groups to carbonyl groups is likely to activate cathodic reactivities, that is, electrophilic reactivities of the carbonyl groups effectively.

### Conclusion

The results described in the present study demonstrate that the reactions of **2** and **5** with Grignard reagents provide a useful tool for preparation of ketones and esters from acid chlorides and chloroformates, respectively. The method with **2** appears superior to that with **5** due to simplicity of the procedure as well as greater product yields. However, employing **5** in place of **2** provides a useful solution for some problems encountered with the method employing **2**. The coupling of **5** with Grignard reagents followed by dephosphorylation under aqueous basic conditions is expected to complement the reactions of **2** with organometallic reagents as a feasible access to carbonyl compounds.

### Experimental

All reactions including air or moisture sensitive reagents were carried out under a nitrogen atmosphere. Dehydrated tetrahydrofuran (THF), toluene, and EtOH were purchased from Kanto Chemical Co., Inc. All Grignard reagents, PhLi, and MeLi were obtained as THF, cyclohexane-ether, and ether solutions, respectively. All other chemicals were of reagent grade, and were used without further purification. For column chromatography, SiO<sub>2</sub> (Wakogel C-20) was used. Melting points were measured on Yanagimoto micro-melting point apparatus, and were not corrected. IR spectra were taken on a JASCO Valor-III spectrometer. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were obtained at 500 and 125 MHz, respectively on a JEOL JNM-LA500 spectrometer, in CDCl<sub>3</sub> with tetramethylsilane as an internal standard. Splitting patterns are designated as "s, d, t, q, and m," indicating "singlet, doublet, triplet, quartet, and multiplet," respectively. Gas-liquid chromatography (GLC) was performed on a Shimadzu GC-8A gas chromatograph with a Shimadzu CBP20 capillary column (length, 25 m; film thickness, 0.25 μm; id, 0.22 mm). Cyclic voltammetry was conducted with a Huso Model 315A potentiostat equipped with a Riken Denshi X-Y recorder. A three electrode configuration was employed: a glassy carbon-disk (7.07 mm<sup>2</sup>) as the working electrode, a saturated calomel electrode (SCE) through an agar bridge as the reference electrode, and a platinum wire as the counter electrode. The fabrication of the glassy carbon electrode has been described previously.<sup>27</sup>

#### *Preparation of dialkyl acylphosphonates (5) and diisopropyl acylphosphonates (6)*

As reported in the literature,<sup>3</sup> a Michaelis-Arbuzov reaction of an acid chloride (**1**) with (EtO)<sub>3</sub>P or (iso-PrO)<sub>3</sub>P, and distillation of the resulting mixture under reduced pressure gave pure **5** or **6**.

**Diethyl benzoylphosphonate (5a).**<sup>3a,b</sup> This compound was obtained from benzoyl chloride (10.0 g, 71 mmol) and (EtO)<sub>3</sub>P (11.8 g, 74 mmol) in 90 % yield. A yellow oil, bp 127-130 °C/4 mmHg. IR (KBr): 1656, 1256, 1020 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.38 (6H, t, *J*=7.3 Hz), 4.25-4.32 (4H, m), 7.52 (2H, t, *J*=7.3 Hz), 7.64 (1H, t, *J*=7.3 Hz), 8.28 (2H, d, *J*=7.3 Hz). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 16.38 (2C, q), 63.99 (2C, dt, <sup>2</sup>*J*<sub>PC</sub>=7 Hz), 128.86 (2C, d), 129.85 (2C, d), 134.77 (d), 135.63 (d, <sup>2</sup>*J*<sub>PC</sub>=74 Hz), 199.07 (d, *J*<sub>PC</sub>=174 Hz). HR-EI-MS, calcd. for C<sub>11</sub>H<sub>15</sub>O<sub>4</sub>P (M<sup>+</sup>) 242.0708, found 242.0696.

**Diethyl acetylphosphonate (5b).**<sup>10b</sup> This compound was obtained from acetyl chloride (7.85 g, 0.1 mol) and (EtO)<sub>3</sub>P (16.6 g, 0.1 mol) in 88% yield. A colorless oil, bp 100-103 °C/8 mmHg. IR (KBr): 1699, 1254, 1022 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.39 (6H, t, *J*=7.3 Hz), 2.49 (3H, d, *J*=4.9 Hz), 4.20-4.27 (4H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 16.25 (2C, dq, <sup>3</sup>*J*<sub>PC</sub>=6 Hz), 30.39 (dq, <sup>2</sup>*J*<sub>PC</sub>=60 Hz), 63.64 (2C, dt, <sup>2</sup>*J*<sub>PC</sub>=7 Hz), 208.75 (d, *J*<sub>PC</sub> = 172 Hz). HR-EI-MS, calcd. for C<sub>6</sub>H<sub>13</sub>O<sub>4</sub>P (M<sup>+</sup>) 180.0551, found 180.0543.

**Diethyl propionylphosphonate (5c).**<sup>10b,28</sup> This compound was obtained from propionyl chloride (4.63 g, 50 mmol) and (EtO)<sub>3</sub>P (8.31 g, 50 mmol) in 80% yield. A colorless oil, bp 99-100 °C/7 mmHg. IR (KBr): 1699, 1254, 1024 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.10 (3H, t, *J*=7.3 Hz), 1.36-1.40 (6H, m), 2.85-2.90 (2H, m), 4.19-4.26 (4H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 6.26 (dq, <sup>3</sup>*J*<sub>PC</sub>=4 Hz), 16.28 (2C, dq, <sup>3</sup>*J*<sub>PC</sub>=6 Hz), 36.69 (dt, <sup>2</sup>*J*<sub>PC</sub>=55 Hz), 63.56 (2C, dt, <sup>2</sup>*J*<sub>PC</sub>=7 Hz), 211.4 (d, *J*<sub>PC</sub>=172 Hz). HR-EI-MS, calcd. for C<sub>7</sub>H<sub>15</sub>O<sub>4</sub>P (M<sup>+</sup>) 194.0708, found 194.0713.

**Diethyl decanoylphosphonate (5d).** This compound was obtained from decanoyl chloride (9.54 g, 50 mmol) and (EtO)<sub>3</sub>P (8.31 g, 50 mmol) in 73% yield. A colorless oil, bp 121-122 °C/2 mmHg. IR (KBr): 1698, 1254, 1021 cm<sup>-1</sup>. <sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.88 (3H, t, *J*=7.0 Hz), 1.22-1.33 (12H, m), 1.36-1.40 (6H, m), 1.59-1.66 (2H, m), 2.83 (2H, t, *J*=7.3 Hz), 4.19-4.25 (4H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 14.09 (q), 16.43 (2C, dq, *J*=6 Hz), 22.44 (dd, <sup>3</sup>*J*<sub>PC</sub>=4 Hz), 22.68 (t), 28.96 (t), 29.25 (t), 29.31 (t), 29.384 (t), 31.87 (t), 43.43 (dt, <sup>2</sup>*J*<sub>PC</sub>=55 Hz), 63.69 (2C, dt, <sup>2</sup>*J*<sub>PC</sub>=7 Hz), 211.34 (d, *J*<sub>PC</sub>=165 Hz). HR-EI-MS, calcd. for C<sub>14</sub>H<sub>29</sub>O<sub>4</sub>P (M<sup>+</sup>) 292.1803, found 292.1794.

**Diethyl 3-phenylpropionylphosphonate (5e).** This compound was obtained from 3-phenylpropionyl chloride (6.24 g, 37 mmol) and (EtO)<sub>3</sub>P (6.15 g, 37 mmol) in 79% yield. A colorless oil, bp 131-133 °C/2 mmHg. IR (KBr): 1698, 1254, 1021 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.35 (6H, t, *J*=7.3 Hz), 2.94 (2H, t, *J*=7.3 Hz), 3.17 (2H, t, *J*=7.3 Hz), 4.16-4.23 (4H, m), 7.17-7.21 (3H, m), 7.26-7.30 (2H, m). <sup>13</sup>C-NMR(CDCl<sub>3</sub>): δ: 16.43 (2C, q), 28.37 (dt, <sup>3</sup>*J*<sub>PC</sub>=6 Hz), 44.91 (dt, <sup>2</sup>*J*<sub>PC</sub>=53 Hz), 63.80 (2C, dt, <sup>2</sup>*J*<sub>PC</sub>=7 Hz), 126.34 (d), 128.35 (2C, d), 128.57 (2C, d), 140.13 (s), 210.26 (d, *J*<sub>PC</sub> =169 Hz). HR-EI-MS, calcd. for C<sub>13</sub>H<sub>19</sub>O<sub>4</sub>P (M<sup>+</sup>) 270.1021, found 270.1022.

**Diethyl ethoxycarbonylphosphonate (5f).** This compound was obtained from ethyl chloroformate (5.43 g, 50 mmol) and (EtO)<sub>3</sub>P (8.31 g, 50 mmol) in 91% yield. A colorless oil, bp 72-74 °C/2 mmHg. IR (KBr): 1714, 1218, 1021 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.34-1.38 (3H, m), 1.38-1.42 (6H, m), 4.27-4.36 (6H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 14.08 (q), 16.29 (2C, dq, <sup>3</sup>*J*<sub>PC</sub>=6 Hz), 62.04 (dt, <sup>3</sup>*J*<sub>PC</sub>=4 Hz), 64.48 (2C, dt, <sup>2</sup>*J*<sub>PC</sub>=7 Hz), 166.95 (d, *J*<sub>PC</sub>=269 Hz). HR-EI-MS, calcd. for C<sub>7</sub>H<sub>15</sub>O<sub>5</sub>P (M<sup>+</sup>) 210.0657, found 210.0674.

*Diisopropyl benzoylphosphonate (6a).*<sup>3a,9</sup> This compound was obtained from benzoyl chloride (5.62 g, 40 mmol) and (iso-PrO)<sub>3</sub>P (8.33 g, 40 mmol) in 34% yield. A yellow oil, bp 133–135 °C/3 mmHg. IR(KBr): 1658, 1252, 996 cm<sup>-1</sup>. <sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.36–1.39 (12H, m), 4.79–4.89 (2H, m), 7.50 (2H, t, *J* = 7.3 Hz), 7.60–7.64 (1H, m), 8.28 (2H, d, *J* = 7.9 Hz). <sup>13</sup>C-NMR(CDCl<sub>3</sub>): δ 23.84 (2C, dq, <sup>3</sup>J<sub>PC</sub> = 6 Hz), 24.09 (2C, dq, <sup>3</sup>J<sub>PC</sub> = 4 Hz), 73.09 (2C, dd, <sup>2</sup>J<sub>PC</sub> = 7 Hz), 128.75 (2C, d), 129.85 (2C, d), 134.49 (d), 135.73 (d, <sup>2</sup>J<sub>PC</sub> = 64 Hz), 199.63 (d, *J*<sub>PC</sub> = 178 Hz). HR-EI-MS, calcd. for C<sub>13</sub>H<sub>19</sub>O<sub>4</sub>P (M<sup>+</sup>) 270.1021, found 270.1020.

*Diisopropyl acetylphosphonate (6b).* This compound was obtained from acetyl chloride (3.14 g, 40 mmol) and (iso-PrO)<sub>3</sub>P (8.33 g, 40 mmol) in 72% yield. A colorless oil, bp 115–117 °C/20 mmHg. IR (KBr): 1702, 1251, 998 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.38 (12H, d, *J* = 6.2 Hz), 2.47 (3H, d, *J* = 4.9 Hz), 4.74–4.84 (2H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 23.86 (2C, dq, <sup>3</sup>J<sub>PC</sub> = 4 Hz), 24.11 (2C, dq, <sup>3</sup>J<sub>PC</sub> = 4 Hz), 30.36 (dq, <sup>2</sup>J<sub>PC</sub> = 59 Hz), 72.90 (2C, dd, <sup>2</sup>J<sub>PC</sub> = 7 Hz), 209.44 (d, *J*<sub>PC</sub> = 172 Hz). HR-EI-MS, calcd. for C<sub>8</sub>H<sub>17</sub>O<sub>4</sub>P (M<sup>+</sup>) 208.0864, found 208.0856.

*Diisopropyl propionylphosphonate (6c).* This compound was obtained from propionyl chloride (3.70 g, 40 mmol) and (iso-PrO)<sub>3</sub>P (8.33 g, 40 mmol) in 78% yield. A colorless oil, bp 121–124 °C/20 mmHg. IR (KBr): 1702, 1251, 998 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.08–1.12 (3H, m), 1.37 (12H, d, *J* = 6.1 Hz), 2.84–2.89 (2H, m), 4.74–4.84 (2H, m). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 6.50 (q), 23.87 (2C, dt, <sup>3</sup>J<sub>PC</sub> = 6 Hz), 24.13 (2C, t), 36.55 (dt, <sup>2</sup>J<sub>PC</sub> = 55 Hz), 72.79 (2C, dd, <sup>2</sup>J<sub>PC</sub> = 7 Hz), 212.06 (d, *J*<sub>PC</sub> = 169 Hz). HR-EI-MS, calcd. for C<sub>9</sub>H<sub>19</sub>O<sub>4</sub>P (M<sup>+</sup>) 222.1021, found 222.1024.

#### *General Procedure of the reactions of Grignard and organolithium reagents with 2*

Bu<sub>3</sub>P (3.3 mmol) was added to a THF solution of **1** (3.0 mmol) cooled to -22 °C in a dry ice-CCl<sub>4</sub> bath, and the resulting mixture was stirred for 20 min. A THF solution of Grignard or organolithium reagent (3.0 mmol) was then added via a syringe. After stirring for 10 min at the same temperature, the reaction was quenched by the addition of 1M aq. HCl (5 ml). The mixture was then poured into 1M aq. HCl (100 ml) and extracted with ether (100 ml x 2). The combined organic layer was washed with 10% aq. K<sub>2</sub>CO<sub>3</sub> (50 ml) and brine (100 ml), dried over MgSO<sub>4</sub>, and evaporated in vacuo. The residue was subjected to column chromatography (hexane-ethyl acetate) to afford the products, or analyzed by GLC. All isolated products were identifiable and gave satisfactory <sup>1</sup>H-NMR and IR spectra. The peaks observed on GLC coincided well with those of authentic samples.

#### *General procedure of the reactions of Grignard or organolithium reagents with 5a*

A THF solution of Grignard or organolithium reagent (3.3 mmol) was added gradually via a syringe to a THF solution of **5a** (3.0 mmol) cooled to -78 °C in a dry ice-acetone bath, and the resulting mixture was stirred for 10 min at the same temperature. The reaction was quenched by the addition of sat. aq. NH<sub>4</sub>Cl (5 ml). The mixture was poured into sat. aq. NH<sub>4</sub>Cl (100 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 ml x 2). The combined organic layer was washed with brine (100 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated in vacuo. The residue was subjected to column chromatography (hexane-ethyl acetate or CH<sub>2</sub>Cl<sub>2</sub>-acetone-AcOH) to afford the products, or analyzed by GLC to determine the yield of **8b**.

**Diethyl 1,1-diphenyl-1-hydroxymethylphosphonate (7a).** White crystals, mp. 115–117 °C (CHCl<sub>3</sub>-hexane). IR(KBr): 3400–2800 (br), 1234, 1054 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.15–1.18 (6H, m), 3.48 (1H, s, OH), 3.85–3.94 (2H, m), 3.96–4.05 (2H, m), 7.24–7.28 (2H, m), 7.30–7.34 (4H, m), 7.68 (4H, d, *J*=7 Hz). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 16.27 (2C, dq, <sup>3</sup>J<sub>PC</sub>=6 Hz), 63.60 (2C, dt, <sup>2</sup>J<sub>PC</sub>=7 Hz), 78.50 (d, *J*<sub>PC</sub>=161 Hz), 127.27 (4C, dd, *J*=6 Hz), 127.57 (2C, d), 127.96 (4C, d), 141.63 (2C, d, <sup>2</sup>J=4 Hz). HR-EI-MS, calcd. for C<sub>17</sub>H<sub>21</sub>O<sub>4</sub>P (M<sup>+</sup>) 320.1177, found 320.1183.

**Diethyl 1-hydroxy-1-phenylethylphosphonate (7b).** White crystals, mp. 74–75 °C (benzene-hexane). IR (KBr): 3500–3100 (br), 1222, 1026 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.18–1.22 (3H, m), 1.24–1.28 (3H, m), 1.82 (3H, d, *J*=15.9 Hz), 3.85–3.95 (1H, m), 3.95–4.03 (1H, m), 4.03–4.14 (2H, m), 7.26–7.30 (1H, m), 7.34–7.38 (2H, m), 7.60 (2H, d, *J*=7.9 Hz). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 16.34 (2C, dq, <sup>3</sup>J<sub>PC</sub>=6 Hz), 25.94 (C, q), 63.24 (dt, <sup>2</sup>J<sub>PC</sub>=7 Hz), 63.32 (dt, <sup>2</sup>J<sub>PC</sub>=7 Hz), 73.51 (d, *J*<sub>PC</sub>=158 Hz), 125.92 (2C, dd, *J*<sub>PC</sub>=4 Hz), 127.35 (d), 127.94 (2C, dd, *J*<sub>PC</sub>=4 Hz), 141.15 (s). HR-EI-MS, calcd. for C<sub>12</sub>H<sub>19</sub>O<sub>4</sub>P (M<sup>+</sup>) 258.1021, found 258.1033.

#### General procedure of the ketone synthesis with 5 or 6

A Grignard reagent was added gradually by a syringe to a THF, DME, or toluene solution of **5** or **6** (3.0 mmol) cooled to -78°C in a dry ice-acetone bath, and the resulting mixture was stirred for 10 min at the same temperature. The reaction was quenched by the addition of sat. aq. NH<sub>4</sub>Cl (5 ml). The mixture was poured into sat. aq. NH<sub>4</sub>Cl (100 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 ml x 2). The combined organic layer was washed with brine (100 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated in vacuo. The residue was treated with 0.1 N aq. NaOH (30 ml)-DME (15 ml) or a dehydrated EtOH (15 ml) solution of NaOH (3 mmol) for 1 h at room temperature. The reaction was quenched by addition of 1 N aq. HCl (3 ml). The mixture was poured into water (100 ml) and extracted with ether (100 ml x 2). The organic layer was washed with brine (100 ml), dried over MgSO<sub>4</sub>, and evaporated in vacuo. The residue was subjected to column chromatography (hexane-ethyl acetate) to afford the products, or analyzed by GLC. All isolated products were identifiable and gave satisfactory <sup>1</sup>H-NMR and IR spectra. The peaks observed on GLC coincided well with those of authentic samples.

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