## Novel Cobalt(0)- or Magnesium-Mediated Approaches to β-Ketophosphonates

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**Abstract:** Two novel approaches to  $\beta$ -ketophosphonates, based on cobalt(0)- or magnesium-mediated reactions of  $\alpha$ -halophosphonates with esters are described.

Key words:  $\beta$ -ketophosphonates, organomagnesium compounds, organocobalt compounds

β-Ketophosphonates, phosphonic analogues of β-keto esters, are one of the very important class of organic compounds. Their complexing ability has been exploited for selective metal extraction.<sup>1</sup> Furthermore they have found several applications as organic intermediates. Examples are the homologation of carbonyl compounds to α,β-unsaturated derivatives via the Horner–Emmons reaction;<sup>2</sup> the synthesis of difficult-to-prepare complex phosphonates, such as phosphorylated heterocyclic compounds;<sup>3</sup> the synthesis of chiral β-hydroxyphosphonic acids, important surrogates for the corresponding carboxylic acids;<sup>4</sup> and the synthesis of β-amino phosphonic acids, important antimetabolites of amino acids.<sup>5</sup>

Many synthetic approaches to  $\beta$ -ketophosphonates, that not general and suffering from limitations, have been developed. The reaction of  $\alpha$ -haloketones with trialkyl phosphites<sup>6</sup> (Michaelis-Arbuzov reaction) or with metallated dialkyl phosphites<sup>7</sup> (Michaelis–Becker reaction) is restricted to highly reactive  $\alpha$ -haloketones and generally gives a mixture of isomers ( $\beta$ -ketophosphonates,  $\alpha$ , $\beta$ -epoxyphosphonates, and enol phosphates). The use of masked carbonyls<sup>8</sup>, although successful, is limited by the availability of starting reagents. The Claisen condensation between  $\alpha$ -lithiumalkyl phosphonates and esters<sup>9</sup> give a mixture of  $\beta$ -ketophosphonates and alkyl phosphonates, due to the higher acidity of the former with respect to the latter. Also attack of the  $\alpha$ -metallated phosphonate on the carbonyl carbon of \beta-ketophosphonate has been observed.<sup>10,11</sup> In any case, α-lithiumalkyl phosphonates require low temperatures, strictly anhydrous media and strong bases such as butyllithium for their preparation. The modified version using organocopper reagents<sup>12</sup> overcomes the acid-base exchange but requires acid chlorides and a large amount of butyllithium, which makes the procedure less convenient in terms of safety and costs.

In an approach related to malonic synthesis,  $\beta$ -ketophosphonates have been obtained by reaction of acid chlorides

Synthesis 2002, No. 12, Print: 06 09 2002. Art Id.1437-210X,E;2002,0,12,1683,1688,ftx,en;P01302SS.pdf. © Georg Thieme Verlag Stuttgart · New York ISSN 0039-7881 (as well as anhydrides or imidazolides) in the presence of magnesium chloride/triethylamine, followed by decarboxylation: this last step, however, may require heating with strong aqueous acids, not recommended for sensitive substrates.<sup>13</sup> Furthermore reactions are slow and heating, that speeds the substrate transformation, also entails side products formation. A further, different approach is based on the reaction of organometallic reagents (such as organocuprates or organolithiums) with 2-dialkylphosphonoalkanoyl chlorides from  $\alpha$ -lithiumalkyl phosphonates.<sup>14</sup> Other miscellaneous approaches include: base-induced isomerization of enol phosphates; reaction of ketone enolates with dialkyl phosphorochloridrites, followed by oxidation;<sup>15</sup> acylation of 1-(trimethylsilyl)vinyl phosphonates.<sup>17</sup>

In this paper we discuss two novel protocols for the synthesis of  $\beta$ -ketophosphonates based on the reaction of  $\alpha$ -halophosphonates with esters: in one case the reactions were promoted by a soluble Co(0) complex; in the other case by magnesium metal (Scheme 1).

The above mentioned Co(0) complexes have been already successfully used to promote Reformatsky-type<sup>18</sup> and aldol-type<sup>19</sup> reactions and are easily prepared from Co(II) salts by reduction with magnesium metal in the presence of a selected phosphine.<sup>20</sup> They can be used either in stoichiometric or in substoichiometric (catalytic) amounts, provided, in the latter case, magnesium metal is present, to carry out the reduction from Co(II) to Co(0).

$$R \xrightarrow{O} P \xrightarrow{O} P \xrightarrow{C} OEt$$

$$R \xrightarrow{O} P \xrightarrow{C} OEt$$

$$R \xrightarrow{O} P \xrightarrow{O} OEt$$

$$OEt$$

$$OE$$

$$OEt$$

$$OE$$

#### Scheme 1

To define the role of the metal and to optimize the experimental conditions and the yields of the reactions, three series of experiments were carried out. Firstly a Co-mediated, 'stoichiometric' procedure was considered: the halophosphonate and the ester were simultaneously added to a tetrahydrofuran solution of the Co(0)-complex at room temperature. The optimum halophosphonate/Co(0)-complex/ester ratio was 2.0:2.0:1.0: a lower halophosphonate/ Co(0)-complex/ester ratio gave lower yields. The best results were obtained with a one-pot procedure, adding the two organic reagents simultaneously to the Co(0) complex.

In the second series of experiments, ('substoichiometric' procedure) a halophosphonate/Co(0)-complex/ester ratio 10:1:10 was used and the reaction was performed in the presence of magnesium metal. In both series of experiments diethyl  $\alpha$ -iodomethylphosphonate, already successfully used in Reformatsky-type reactions, and the Co(0)-complex with trimethylphosphine were first used; the solid, easier-to-handle triphenylphosphine can be used as well as a ligand to the metal.

In the third series of experiments, the  $\alpha$ -halophosphonate and the ester were added to magnesium alone in tetrahydrofuran under the same experimental conditions used for the Co-mediated reactions under 'substoichiometric' conditions (speed of stirring, temperature, dilution, etc.).

The results are summarized in the Table and deserve few comments. A variety of ester structural forms are tolerated in this reaction. The desired  $\beta$ -ketophosphonates are generally obtained in reasonable to good yields (45-90%), depending on the substrate and on the protocol used. With esters containing a nitrogen atom elsewhere, the reaction was less efficient, as exemplified by 2-carbomethoxypyridine which gave the lowest yields (34–39% at the best in Co-mediated reactions). The Co-mediated reaction was not practicable with  $\alpha,\beta$ -unsaturated esters, which gave mixtures of unidentified products. Concurrent attack of the organometallic reagent on the carbonyl carbon of the formed  $\beta$ -ketophosphonate was not observed, even in the presence of the reagent in excess. Besides the  $\beta$ -ketophosphonate, the only other compounds observed in the reaction mixture were unreacted starting ester and diethyl methanephosphonate.<sup>21</sup> The former was easily separated by chromatography and recycled. In most cases a simple filtration on a very short column of silica gel was enough; a procedure easily applicable also if the reaction has to be scaled up.

Comparing the Co-mediated reactions, the 'stoichiometric' procedure can be the protocol of choice for substrates with delicate, highly-magnesium sensitive, functionalities; but there is no doubt that, in general, the 'substoichiometric' procedure is more convenient: it is not necessary to filter-off the magnesium; the amounts of cobalt and phosphines are minimized (thus offsetting the disadvantage of their use); the workup of the reaction and the purification of the products are easier and, as a consequence, a higher recovery of products may be observed. Furthermore the course and the end point of the reaction are easily monitored by the alternation of the brown color of the Co(0)-complex and the blue-violet color of the Co(II)complex during the addition of the  $\alpha$ -halophosphonate/ester reagents to the Cobalt-complex.<sup>22</sup>

The reactions performed with magnesium alone, in the absence of cobalt, were less reproducible and required a variable period of induction. Once started, the reactions gave the expected  $\beta$ -ketophosphonates in variable amounts depending on the ester. These results indicate that in the absence of Co-complex, magnesium alone is capable of giving  $\beta$ -ketophosphonates from halophosphonates and ester with equal, or better efficiency in some cases, albeit in a less predictable way.

Whereas there is no doubt on the key role played by cobalt in the 'stoichiometric' procedure, the observation that magnesium on its own mediates the reactions, could arouse doubts on the role of cobalt in the 'substoichiometric' conditions. However, in addition to the different reaction speed and reproducibility observed in the presence or in the absence of the Co(0)-complex (higher in the former case), one more piece of evidence that might prove the actual involvement of cobalt, also under 'substoichiometric' conditions, is the color of the solution which, as reported above, continuously changes during the addition of the organic reagents. It is therefore reasonable to assume that, as far as the reduction Co(II)/Co(0) is faster than the reaction of magnesium with the  $\alpha$ -halophosphonate, the soluble Co(0)-complex reacts with the  $\alpha$ -halophosphonate before magnesium, that must work in heterogeneous phase.

In conclusion we have presented two novel procedures for the synthesis of  $\beta$ -ketophosphonates via a Reformatskytype addition of  $\alpha$ -halophosphonates to esters. In one procedure the reactions are performed using a catalytic amount of a soluble Co(0)-complex in the presence of magnesium metal. In the other procedure magnesium metal alone is used.

In general, the reactions proceed with comparable efficiency with both procedures; in few cases better yields were obtained with magnesium metal alone, but this metal works in a less reproducible way due to the heterogeneous conditions and to the requirement of the metal activation. Advantages of these cobalt- and/or magnesium methodologies with respect to known procedures are: mild reaction conditions and easily available carbonyl substrates; no strong bases, acids or heat required; lower costs and higher safety; reagents easier to be handled and stored; and no side products deriving from the attack on the carbonyl carbon of the  $\beta$ -ketophosphonate are formed. When cobalt is used, an added advantage, which also makes the cobaltprocedure more valuable, is the color of the solution, which provides an efficient monitoring of the course of the reaction and allows a timely visualization of its end point with minimization of byproducts.

Anhyd THF from Aldrich was generally used. With Mg-mediated reactions, reagent grade THF was refluxed over  $\text{LiAlH}_4$  and distilled before use. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at 200 and 300 MHz on Bruker spectrometers. MS spectra were recorded on a VG7070 E9 spectrometer. Flash-column chromatography was performed on silica gel (Merck Kieselgel 60, 230–400 mesh). TLC was performed on silica gel plates (60 F254, Merck), spots were detected visually by ultraviolet irradiation (254 nm) or by spraying with MeOH–H<sub>2</sub>SO<sub>4</sub> (9:1), followed by heating at 100 °C. All reactions were performed under dry N<sub>2</sub>, using glassware dried by flaming in a stream of dry N<sub>2</sub>. Petroleum ether used had bp 40–60°C.

Entry	Ester	Product	Yield (%)	Procedure <sup>a</sup>
1	0 	O O       ∠OEt	51 (22) <sup>b</sup> 63 (11) <sup>b</sup>	A B
	Ph OMe 1a	Ph P OEt	37 (49) <sup>b</sup>	С
2		$\begin{array}{c} O & O \\    &    \\ P & OEt \end{array}$	46 (40) <sup>b</sup> 70 (22) <sup>b</sup> 45 (42) <sup>b</sup>	A B C
	PhCH <sub>2</sub> OMe <b>1b</b>	$PhCH_2 \rightarrow OEt$ <b>2b</b>	43 (42)	C
3	PhCH <sub>2</sub> CH <sub>2</sub> OMe	$PhCH_2CH_2$ $P$ $OEt$ $OEt$ $OEt$	- 83 90°	A B C
4		$\begin{array}{ccc} \mathbf{2c} & & \\ & & \mathbf{O} & \mathbf{O} \\ \parallel & \parallel & \mathbf{OEt} \end{array}$	mixture of products 56	В
	MeCH=CH OMe 1d	MeCH=CH OEt		С
5	O II	$O O O \parallel \square OEt$	mixture of products 30	А
	PhCH=CH OMe 1e	PhCH=CH OEt		С
6	O OMc	O O I V OEt OEt	57	В
7		$2f \qquad 0 \qquad 0 \\ \downarrow \qquad 0 \\ \downarrow \qquad 0 \\ P \\ OEt$	57 85°	B C
8	1g O U OMe	2g $O O O$ $P OEt$ $OEt$	56 80°	B C
9	<b>1h</b> O	$\begin{array}{ccc} \mathbf{2h} \\ O & O \\ I & I & OEt \end{array}$	53 47	B C
	<sup>t</sup> Bu OMe	$r_{Bu} \sim P \sim OEt$ 2i		
10			34 (55) <sup>b</sup> 39 14 (15) <sup>b</sup>	A B C
	0 1j	0 0 2j		

Table Reactions Between Ethyl a-Iodomethylphosphonate and Esters

<sup>a</sup> Procedure A (stoichiometric): ester, ethyl  $\alpha$ -iodomethylphosphonate and [Co(PMe<sub>3</sub>)]<sub>4</sub> were used in a 1:2.0:2.0 ratio. Procedure B (substoichiometric): the reaction was performed using a substoichiometric quantity of Co(PMe<sub>3</sub>)<sub>4</sub> (10–15%). Procedure C: the reaction was performed using metallic Mg only.

<sup>b</sup> The amount given in parenthesis refers to recovered starting ester.

<sup>c</sup> Yields determined by <sup>1</sup>H NMR spectroscopy.

# Stoichiometric Reaction Mediated by $(\ensuremath{Me_3}\ensuremath{P})_4\ensuremath{Co}\xspace;$ General Procedure

*Procedure A*: A 1 M solution of Me<sub>3</sub>P in THF (10 mL) was added to a mixture of activated Mg turnings<sup>23,24</sup> (0.3 g) and anhyd CoCl<sub>2</sub> (0.26 g, 2.0 mmol). The reaction mixture was stirred at r.t. till a dark brown color developed.<sup>25</sup> The excess of Mg was filtered, and to the resulting solution were added diethyl  $\alpha$ -iodomethylphosphonate (0.32 mL, 2.0 mmol) and the ester (1 mmol) in THF (2–3 mL) dropwise over a period of 1 h. The reaction was monitored by TLC (silica gel, eluent: EtOAc–petroleum ether, 7:3). At the end of the

reaction, the mixture was stirred in the air till a blue color developed. Two different workup procedures were then used depending on the water-solubility of the ester and/or of the product. For waterinsoluble compounds the reaction mixture was diluted with EtOAc and poured into 5% aq HCl (2-3 mL). The aqueous phase was extracted with EtOAc ( $3 \times 15$  mL). The organic layers were collected, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to dryness. Occasionally a light blue or green color still persistent in the crude material was eliminated by dissolving in EtOAc and by washing with a sat. EDTA (bis-sodium salt) solution. For partially soluble-compounds, the reaction mixture was filtered on silica gel eluting with EtOAc-petroleum ether to remove cobalt salts. The crude material was chromatographed on silica gel, eluting with EtOAc-petroleum ether mixtures of increasing polarity, to separate the product from the unreacted starting ester. Me<sub>3</sub>P can be substituted by Ph<sub>3</sub>P withouth affecting the course of the reactions.

## Substoichiometric Reaction Mediated by $(Me_3P)_4Co$ ; General Procedure

*Procedure B*: A 1 M solution of Me<sub>3</sub>P in anhyd THF (1 mL) was added to a mixture of activated Mg (0.2 g) and anhyd CoCl<sub>2</sub> (0.019 g, 0.15 mmol). The mixture was stirred at r.t. till the brown color of the cobalt(0) complex had developed. To the mixture, a THF solution (3 mL) of ester (1 mmol) and diethyl α-iodomethylphosphonate (0.334 g, 1.2 mmol) was added dropwise under stirring. The speed of addition was modulated so as to reduce the time of persistence of the blue color [Co(II) complex] developed during the addition to a minimum. At the end of the reaction, indicated by the persistence of the brown color of the original Co(0) complex, the Mg was filtered and the resulting solution was stirred in air till a blue color developed. The reaction mixture was then treated as described above for the stoichiometric procedure. Me<sub>3</sub>P can be substituted by Ph<sub>3</sub>P without affecting the course of the reactions.

#### Reaction Mediated by Magnesium; General Procedure

*Procedure C*: To a suspension of activated Mg turnings (0.3 g) in freshly distilled anhyd THF (2 mL) was added dropwise a THF solution (3 mL) of ester (1 mmol) and diethyl  $\alpha$ -iodomethyl phosphonate (0.334 g, 1.2 mmol). The reaction was monitored by TLC (silica gel, eluent: EtOAc–petroleum ether). The Mg was filtered and the resulting solution was treated according to one of the two procedures described in the previous section, depending on the water solubility of the product.

#### 2a

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.25 (t, 6 H, J = 7.8 Hz), 3.6 (d, 2 H,  $J_{\rm CP}$  = 23.7 Hz), 4.1 (dq, 4 H, J = 7.8 Hz), 7.4–7.62 (m, 3 H), 7.97 (dd, 2 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 16.07 (dq,  $J_{CP}$  = 16.0 Hz), 38.26 (dq,  $J_{CP}$  = 129.55 Hz), 62.50 (dt,  $J_{CP}$  = 5.35 Hz), 2×128.45 (d), 2×129.87 (d), 133.42 (d), 136.55 (s), 191.69 (s).

<sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta = 20.64$ .

MS: m/z = 256 (M<sup>+</sup>), 227 (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>), 211 (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>O), 183 (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>O - CH<sub>2</sub>=CH<sub>2</sub>), 151 [CH<sub>2</sub>P(O)(O C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>].

HRMS: m/z Calcd for  $C_{12}H_{17}O_4P$ : 256.0864476. Found: 256.0906000.

#### **2**b

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.34$  (t, 6 H, J = 6.5 Hz), 3.1 (d, 2 H, J = 23.3 Hz), 3.9 (s, 2 H), 4.15 (dd, 4 H, J = 6.5, 6.5 Hz), 7.15–7.35 (m, 5 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 16.19 (dq, J = 5.28 Hz), 41.30 (dq,  $J_{CP} = 127.61$  Hz), 50.67 (t), 62.53 (dt,  $J_{CP} = 7.29$  Hz), 127.14 (d), 2 × 128.69 (d), 2 × 129.51 (d), 133.42 (s), 199.34 (s).

MS: m/z = 270 (M<sup>+</sup>), 179 (M<sup>+</sup> - CH<sub>3</sub>CH<sub>2</sub>O - CH<sub>3</sub>CH<sub>2</sub>OH), 151 [CH<sub>2</sub>P(O)(OEt)], 137 (151 - CH<sub>2</sub>), 91 (PhCH<sub>2</sub>).

HRMS: m/z Calcd for  $C_{13}H_{19}O_4P$ : 270.1020977200. Found: 270.0995000.

## 2c

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.30 (t, 6 H, *J* = 7.5 Hz), 2.85–2.95 (m, 4 H), 3.05 (d, 2 H, *J*<sub>CP</sub> = 22 Hz), 4.1 (dq, *J*<sub>CP</sub> = 7.5 Hz), 7.15–7.35 (m, 5 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 16.18 (dq, J = 5.18 Hz), 29.35 (t), 42.52 (dq,  $J_{CP}$  = 127.5 Hz), 45.29 (t), 62.40 (dt,  $J_{CP}$  = 5.48 Hz), 2 × 126.03 (d), 3 × 128.33 (d), 140.57 (s), 200.94 (s).

<sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta$ = 20.46.

MS: *m*/*z* = 284 (M<sup>+</sup>), 255 (M<sup>+</sup> – CH<sub>3</sub>CH<sub>2</sub>), 179 (M<sup>+</sup> – PhCH<sub>2</sub>CH<sub>2</sub>), 152 [CH<sub>3</sub>P(O)(OEt)<sub>2</sub>], 105 (PhCH<sub>2</sub>CH<sub>2</sub>), 91 (PhCH<sub>2</sub>).

HRMS: m/z Calcd for  $C_{14}H_{21}O_4P$ : 284.1177478000. Found: 284.1186000.

## 2d

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.27 (t, 6 H, *J* = 7.0 Hz), 1.88 (dd, 3 H, *J* = 6.78, 1.8 Hz), 3.15 (d, 2 H, *J* = 22.6 Hz), 4.1 (dq, 4 H, *J* = 7.32 Hz), 6.2 (dq, 1 H, *J* = 14.09, 1.8 Hz), 6.91 (dq, 1 H, *J* = 15.7, 6.9 Hz).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 16.11 (q), 39.8 (dq,  $J_{CP}$  = 128.06 Hz), 62.32 (dq,  $J_{CP}$  = 5.65 Hz), 131.46 (d), 145.26 (d), 140.75 (s), 190.8 (s). <sup>31</sup>P NMR (CDCl<sub>3</sub>): δ= 20.91.

#### 2e

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.32 (t, 6 H, *J* = 6.94 Hz), 3.32 (d, 2 H, *J* = 22.68 Hz), 4.18 (dq, 4 H, *J* = 6.94 Hz), 6.9 (d, 1 H, *J* = 16.03 Hz), 7.21–7.6 (m, 5 H), 7.65 (d, 1 H, *J* = 16.03 Hz).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 16.24 (dq, J = 4.53 Hz), 40.98 (dq,  $J_{CP}$  = 127.9 Hz), 62.55 (dt,  $J_{CP}$  = 4.63 Hz), 125.69 (d), 2 × 128.52 (d), 2 × 128.92 (d), 130.80 (d), 134.12 (s), 144.65 (d), 191.01 (s). <sup>31</sup>P NMR (CDCl<sub>3</sub>): δ = 20.85.

MS:  $m/z = 282 (M^+)$ , 253  $(M^+ - CH_3CH_2)$ , 179  $(M^+ - PhCH=CH)$ , 152  $[CH_3P(O)(OEt)_2]$ , 131  $[M^+ - CH_2P(O)(OEt)_2]$ , 103 (PhCH=CH).

HRMS: m/z Calcd for  $C_{14}H_{19}O_4P$ : 282.1020977. Found: 282.1039000.

#### 2f

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 1.22 (t, 6 H, *J* = 7.0 Hz), 1.10–1.45 (m, 5 H), 1.55–1.64 (m, 1 H), 1.64–1.77 (m, 2 H), 1.77–1.88 (m, 2 H), 2.48– 2.59 (m, 1 H), 3.02 (d, 2 H, *J* = 21.0 Hz), 4.06 (dq, 4 H, *J* = 7.3 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 16.23 (dq, *J* = 5.45 Hz), 2 × 25.41 (t), 25.70 (t), 28.18 (t), 40.21 (dq, *J*<sub>CP</sub> = 117.05 Hz), 41.07 (t), 51.35 (d), 62.38 (dt, *J* = 5.55 Hz), 205.20 (s).

<sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta = 20.99$ .

Anal. Calcd for  $C_{11}H_{23}O_4P$ : C, 54.96; H, 8.78. Found: C, 54.88; H, 8.68.

## 2g

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 0.85 (t, 3 H, *J* = 7.0 Hz), 1.26 (t, 6 H, *J* = 7.0 Hz), 1.20–1.32 (m, 2 H), 1.5 (tt, 2 H, *J* = 7.0, 7.0 Hz), 2.56 (t, 2 H, *J* = 7.0 Hz), 3.01 (d, 2 H, *J* = 23.0 Hz), 4.10 (dq, 4 H, *J* = 7.0 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 13.75 (d), 16.24 (dq, *J* = 4.7 Hz), 22.41 (t), 25.47 (t), 42.31 (dq, *J*<sub>CP</sub> = 83.75 Hz), 2 × 43.73 (t), 62.49 (t), 202.18

(s).

<sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta = 20.67$ .

MS:  $m/z = 236 (M^+)$ , 207  $(M^+ - CH_2CH_3)$ , 179  $[M^+ - CH_3(CH_2)_3]$ , 152  $[CH_3P(O)(OEt)_2]$ , 151  $[CH_2P(O)(OEt)_2]$ , 137  $[P(O)(OCH_2CH_3)]$ , 85  $[M^+ - CH_2P(O)(OEt)_2]$ , 57  $[CH_3(CH_2)_3]$ .

Anal. Calcd for  $C_{10}H_{21}O_4P$ : C, 50.85; H, 8.90. Found: C, 50.55; H, 8.85.

### 2h

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.95$  (dt, 2 H, J = 4.2, 7.2 Hz), 1.1 (dt, 2 H, J = 8.0, 4.4 Hz), 1.3 (t, 6 H, J = 7.0 Hz), 2.18 (tt, 1 H, J = 7.2, 7.2, 4.0, 4.0 Hz), 3.18 (d, 2 H, J = 23.25 Hz), 4.12 (dq, 4 H, J = 7.0 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta = 2 \times 11.96$  (t), 16.46 (dq,  $J_{CP} = 5.13$  Hz), 21.60 Hz)

21.68 (d), 43.54 (dq,  $J_{CP} = 127.86$  Hz), 62.66 (dt,  $J_{CP} = 5.38$  Hz), 202.02 (s).

<sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta = 21.03$ .

MS:  $m/z = 220 (M^+)$ , 191 (M<sup>+</sup> – CH<sub>2</sub>CH<sub>3</sub>), 175 (M<sup>+</sup> – OCH<sub>2</sub>CH<sub>3</sub>), 151 [CH<sub>2</sub>P(O)(OEt)<sub>2</sub>], 69 [M<sup>+</sup> – CH<sub>2</sub>P(O)(OEt)<sub>2</sub>].

HRMS: m/z Calcd for C<sub>9</sub>H<sub>17</sub>O<sub>4</sub>P: 220.0864476. Found: 220.0853000.

## 2i

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.1 (s, 9 H), 1.25 (t, 6 H, *J* = 6 Hz), 3.08 (d, 2 H, *J* = 22 Hz), 4.08 (dq, 4 H, *J* = 6 Hz).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 16.18 (dq,  $J_{CP}$  = 5.56 Hz), 3 × 25.93 (q), 35.69 (dq,  $J_{CP}$  = 134.77 Hz), 45.00 (s), 62.16 (dt,  $J_{CP}$  = 5.59 Hz), 207.00 (s).

<sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta = 21.88$ .

MS:  $m/z = 236 (M^+)$ , 191 (M<sup>+</sup> – OCH<sub>2</sub>CH<sub>3</sub>), 179 (M<sup>+</sup> – *t*-C<sub>4</sub>H<sub>9</sub>), 152 [CH<sub>3</sub>P(O)(OEt)<sub>2</sub>], 151 [CH<sub>2</sub>P(O)(OEt)<sub>2</sub>].

Anal. Calcd for  $C_{10}H_{21}O_4P$ : C, 50.85; H, 8.90. Found: C, 51.01; H, 8.98.

## 2j

Colorless thick oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.28 (t, 6 H, *J* = 5.9 Hz), 4.0 (d, 2 H, *J* = 23.5 Hz), 4.15 (dq, 4 H, *J* = 5.9 Hz), 7.48 (dd, 1 H, *J* = 1.15, 5.75 Hz), 7.83 (d, 1 H, *J* = 2.3, 8.05 Hz), 8.06 (d, 1 H, *J* = 9.2 Hz), 8.69 (d, 1 H, *J* = 4.6 Hz).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 16.40 (dq, J = 5.48 Hz), 36.18 (dq,  $J_{CP} = 130.53$  Hz), 62.60 (dt, J = 5.43 Hz), 122.44 (d), 127.59 (d), 137.16 (d), 149.15 (d), 153.07 (s), 193.89 (s).

<sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta = 21.35$ .

MS: m/z = 257 (M<sup>+</sup>), 212 (M<sup>+</sup> – OCH<sub>2</sub>CH<sub>3</sub>), 179 (M<sup>+</sup> – C<sub>5</sub>H<sub>4</sub>N), 151 [CH<sub>2</sub>P(O)(OEt<sub>2</sub>], 106 [M<sup>+</sup> – CH<sub>2</sub>P(O)(OEt<sub>2</sub>)], 78 (C<sub>5</sub>H<sub>4</sub>N).

HRMS: m/z Calcd for  $C_{11}H_{16}NO_4P$ : 257.0816966080. Found: 257.0822000.

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- (21) Diethyl methanephosphonate may form both from acid-base exchange between the β-ketophosphonate and the αmetallated phosphonate (as observed for lithium phosphonate) or from hydrolysis, most likely during workup, from an unreacted organometallic reagent (as observed in Reformatsky-type reactions).
- (22) This behaviour would suggest a mechanism involving the oxidative addition of the  $\alpha$ -halophosphonate to the cobalt(0)-complex to give a cobalt(II) species, as well as the

substitution of a phosphine ligand by a carbonyl donor group. Reaction between the two organic moieties bound to the cobalt center would then give the product together with a Co(II) species from which the Co(0) precursor would be regenerated by reduction with Mg metal.

- (23) Mg metal is used in excess and can be recycled after use.
- (24) Mg was activated by adding a few drops of 1,2dichloroethane to the metal turnings in THF so that a vigorous reaction ensued. After few minutes the mixture was cooled in an ice-bath, the solvent was removed and the Mg was washed with THF ( $3 \times 2$  mL).
- (25) The solution can be also warmed with an external bath at about 50 °C to speed the reduction of Co(II) to Co(0). Warming may be useful when Ph<sub>3</sub>P is used instead of Me<sub>3</sub>P.