

# The Synthesis of *N,N*-Bis(dialkoxyphosphinoylmethyl)- and *N,N*-Bis(diphenylphosphinoylmethyl)glycine Esters by the Microwave-Assisted Double Kabachnik–Fields Reaction

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**ABSTRACT:** The condensation of a glycine ester, two equivalents of paraformaldehyde, and the same quantity of a dialkyl phosphite or diphenylphosphine oxide afforded the title compounds as new bis(phospha-Mannich) products under microwave (MW) conditions at 100°C. The dialkoxyphosphinoylmethyl derivatives were synthesized under solvent-free conditions, whereas the diphenylphosphinoylmethyl derivatives were synthesized in acetonitrile solution. Comparative thermal experiments showed the beneficial role of MW in respect of efficiency. © 2013 Wiley Periodicals, Inc. *Heteroatom Chem.* 24:510–515, 2013; View this article online at [wileyonlinelibrary.com](http://wileyonlinelibrary.com). DOI 10.1002/hc.21126

## INTRODUCTION

The Kabachnik–Fields reaction of amines, aldehydes, and dialkyl phosphites leading to  $\alpha$ -aminophosphonates [1,2] remains an evergreen reaction model for three reasons. The resulting  $\alpha$ -aminophosphonic derivatives are important targets in the development of antibiotics, antiviral species, antihypertensives, and antitumour agents based on their effect as inhibitors of GABA receptors, enzyme inhibitors, and antimetabolites [3–7].

The mechanism of reaction also generated a considerable interest, in whether imines (Schiff bases) or  $\alpha$ -hydroxyphosphonates are the intermediates of the Kabachnik–Fields reaction [8–11]. The way of accomplishment has also been in focus. More and more catalytic versions and the use of microwave (MW) irradiation were described [12–26]. The senior author of this article (G. Keglevich) suggested that under MW-assisted and solvent-free conditions, there is no need for any catalyst [27]. The Kabachnik–Fields condensation was extended to a wide variety of models including *N*-heterocycles and heterocyclic  $>P(O)H$  species [28, 29].  $\alpha$ -Aminoacid esters were also applied as

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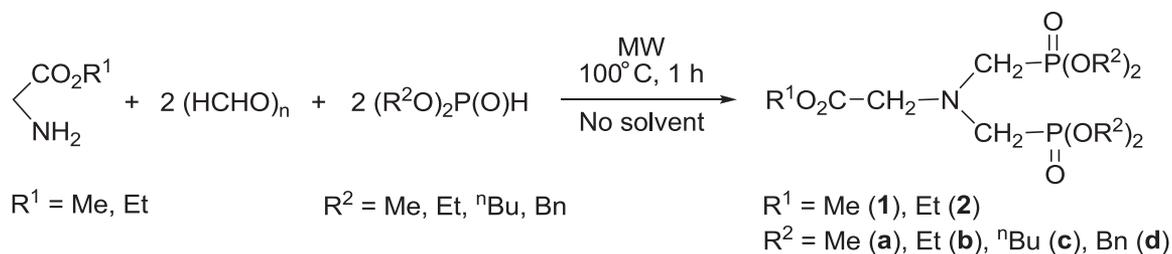
Contract grant sponsor: Hungarian Scientific and Research Fund.

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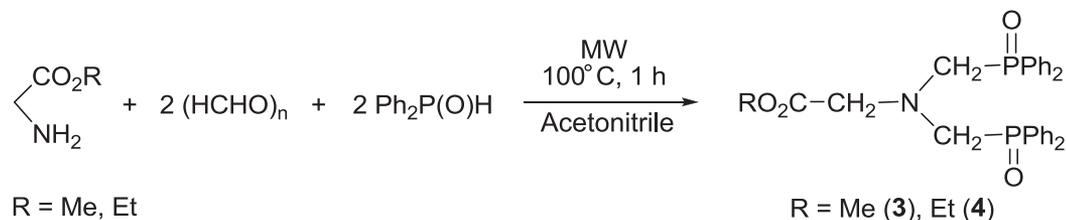
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**SCHEME 1** The double Kabachnik–Fields reaction of glycine esters, paraformaldehyde, and dialkyl phosphites.



**SCHEME 2** The double Kabachnik–Fields reaction of glycine esters, paraformaldehyde, and diphenylphosphine oxide.

starting materials [30–33]. In another research line, primary amines were utilized in the double Kabachnik–Fields reaction resulting in the formation of bis(phosphonomethyl)amine derivatives [34–38]. Another special approach was also described for the synthesis of bis(phospha-Mannich) derivatives [39]. The bis(diphenylphosphinoylmethyl)amines may be regarded as precursors of bisphosphine ligands. The bisphosphines formed after double deoxygenation from the bis(phosphine oxides) may be converted to ring platinum complexes that can be used as catalysts in the hydroformylation of styrene [36–38].

In this article, novel *N,N*-bis(dialkoxyphosphinoylmethyl)- and *N,N*-bis(diphenylphosphinoylmethyl)glycine esters are described utilizing the double Kabachnik–Fields reaction of glycine esters.

## RESULTS AND DISCUSSION

The methyl and ethyl glycine esters liberated from the corresponding hydrochloride salts were reacted with two equivalents of paraformaldehyde and the same amount of dialkyl phosphites including dimethyl phosphite, diethyl phosphite, dibutyl phosphite, and dibenzyl phosphite under MW and solvent-free conditions at 100°C for 1 h. The expected *N,N*-bis(dialkoxyphosphinoylmethyl)glycine esters (**1b**, **1c**, and **2a–d**) were obtained in 70%–94% yield after column chromatography (Scheme 1, Table 1). The similar reaction of diphenylphosphine oxide afforded the bis(diphenylphosphinoylmethyl)

**TABLE 1** Yields of the Bis(>P(O)CH<sub>2</sub>)glycine Esters

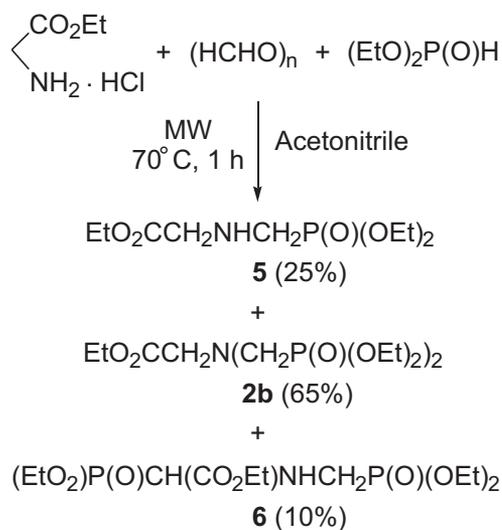
Entry	Compound	Yield (%)
1	<b>1b</b>	85
2	<b>1c</b>	93
3	<b>2a</b>	70
4	<b>2b</b>	87
5	<b>2c</b>	83
6	<b>2d</b>	94
7	<b>3</b>	92
8	<b>4</b>	88

derivatives **3** and **4** in ca. 90% yields. Because of heterogeneity, these reactions had to be carried out in acetonitrile as the solvent (Scheme 2, Table 1).

With the exception of **2b** [35], all other products (**1b**, **1c**, **2a**, **2c**, and **2d**, along with **3** and **4**) are new and were characterized by <sup>31</sup>P, <sup>13</sup>C and <sup>1</sup>H nuclear magnetic resonance (NMR), as well as high-resolution molecular spectroscopy data.

Bisadduct **2b** was also prepared from *N*-(diethoxyphosphinoylmethyl)glycine ethyl ester **5** synthesized separately by its reaction with one equivalent of paraformaldehyde and diethyl phosphite at 100°C for 1 h. After flash column chromatography, product **2b** was obtained in a yield of 93%, which was somewhat better than the outcome of the one-step procedure (87%, Table 1/Entry 4).

Starting from glycine ester hydrochloride instead of the free glycine ester, acetonitrile had to be used as the solvent due to the heterogeneity. After an irradiation of 1 h at 70°C, a mixture



**SCHEME 3** The outcome of the Kabachnik–Fields reaction starting from glycine ester hydrochloride.

containing ca. 50% of the expected product (**2b**) [35] besides unidentified by-products was formed. When the glycine ester hydrochloride was reacted with one equivalent of formaldehyde and the same amount of diethyl phosphite, a mixture of *N*-(diethoxyphosphinoylmethyl)glycine ethyl ester (**5**) [ $\delta_p$  ( $\text{CDCl}_3$ ) 23.7, ( $\delta_p$  [32] 22.9),  $[\text{M} + \text{H}]^+_{\text{found}} = 254.1160$ ,  $\text{C}_9\text{H}_{21}\text{NO}_5\text{P}$  requires 254.1157], *N,N*-bis(diethoxyphosphinoylmethyl)glycine ethyl ester (**2b**) [35] and 2-(diethoxyphosphinoyl)-*N*-(diethoxyphosphinoylmethyl)glycine ethyl ester (**6**) [ $\delta_p$  ( $\text{CDCl}_3$ ) 15.1,  $[\text{M} + \text{H}]^+_{\text{found}} = 390.1457$ ,  $\text{C}_{13}\text{H}_{30}\text{NO}_8\text{P}_2$  requires 390.1447] was formed. The ratio of **5**, **2b**, and **6** was 25:65:10 (Scheme 3). It was somewhat surprising that despite the equimolar ratio of the components, bis(diethoxyphosphinoylmethyl)glycine ester **2b** was the major component. The glycine ethyl ester hydrochloride was not too reactive in the primary Kabachnik–Fields reaction, but once it had been formed, it further reacted easily with formaldehyde and diethyl phosphite.

**TABLE 2** Composition of Comparative Thermal Experiments

Entry	Composition (%)			Isolated Yield of Bis Product (%)
	$\text{R}^1\text{O}_2\text{CCH}_2\text{NHCH}_2\text{P}(\text{O})(\text{OR}^2)_2$	Bis Product	By-product	
1	5 ( $\text{R}^1 = \text{Me}$ , $\text{R}^2 = \text{Et}$ )	84 ( <b>1b</b> )	11	66 ( <b>1b</b> )
2	2 ( $\text{R}^1 = \text{Et}$ , $\text{R}^2 = \text{Me}$ )	91 ( <b>2a</b> )	7	57 ( <b>2a</b> )
3 <sup>a</sup>	30 ( $\text{R}^1 = \text{Et}$ , $\text{R}^2 = \text{Et}$ )	62 ( <b>2b</b> )	8	53 ( <b>2b</b> )

<sup>a</sup>After an additional heating of 2 h, the mixture contained 21% of phosphonomethylglycine ester and 71% of **2b** beside the 8% of the by-product.

### Comparative Thermal Experiments

To evaluate the potential of MW irradiation, comparative thermal experiments were carried out in a few instances at 100°C for 1 h. On conventional heating, mixtures comprising the bis(diethoxyphosphinoylmethyl)glycine ester (**1b**, **2a**, or **2b**) as the major component (61%–91%) and the primary dialkoxyphosphinoylmethylglycine esters [ $\text{R}^1\text{O}_2\text{CCH}_2\text{NHCH}_2\text{P}(\text{O})(\text{OR}^2)_2$ ] as the minor components (2%–30%) were formed (Table 2). A small portion (ca. 9%) of unidentified by-products was also formed. On further heating, only a minor part of the dialkoxyphosphinoylmethylglycine esters was converted to the corresponding bis products (**1b**, **2a**, and **2b**). After purification by column chromatography, bis(diethoxyphosphinoylmethyl)glycines **1b**, **2a**, and **2b** were obtained in preparative yields of 66%, 57%, and 53%, respectively. The incomplete conversions in respect of the bis products (**1b**, **2a**, and **2b**) and the 13%–34% lower yields of the thermal control experiments clearly indicate the advantage of the MW accomplishment. The MW-assisted reactions are generally more efficient than the variations carried out under conventional heating [40–42].

In conclusion, eight bis(diethoxyphosphinoylmethyl)- or bis(diphenylphosphinoylmethyl)glycine esters were synthesized under MW conditions. Among the compounds synthesized, seven are new. The potential of the MW irradiation was proved by comparative thermal experiments.

### EXPERIMENTAL

#### General

The  $^{31}\text{P}$ ,  $^{13}\text{C}$ , and  $^1\text{H}$  NMR spectra were obtained in  $\text{CDCl}_3$  solution on a Bruker AV-300 spectrometer operating at 121.5, 75.5, and 300 MHz, respectively. Chemical shifts are downfield relative to 85%  $\text{H}_3\text{PO}_4$  and tetramethylsilane. Mass spectrometric measurements were performed using a Q-TOF Premier mass spectrometer (Waters Corporation, Milford, Massachusetts) in positive electrospray mode.

The reactions were carried out in a 300 W CEM Discover focused MW reactor (CEM Microwave Technology, Buckingham, UK) equipped with a pressure controller, applying 20–30 W under isothermal conditions.

The glycine esters were liberated from their hydrochloride salts using 20% Na<sub>2</sub>CO<sub>3</sub> solution (2.0 g of Na<sub>2</sub>CO<sub>3</sub> and 8 mL of water). Dichloromethane was used for the extraction of the free base. The organic phase was separated and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the volatile components provided the glycine esters.

### General Procedure for the Preparation of Bis(>P(O)CH<sub>2</sub>)glycine Esters

A mixture of 1.70 mmol glycine ester (0.15 g of glycine methyl ester or 0.18 g of glycine ethyl ester), 0.10 g (3.40 mmol) of paraformaldehyde, and 3.40 mmol of the >P(O)H species (0.31 mL of dimethyl phosphite, 0.44 mL of diethyl phosphite, 0.67 mL of dibutyl phosphite, and 0.75 mL of dibenzyl phosphite) was heated at 100°C in a vial in a CEM Discover Microwave reactor equipped with a pressure controller for 1 h. Then, the water formed was removed in vacuum. Column chromatography (silica gel 3% methanol in dichloromethane) of the residue afforded the products (**1a**, **1b**, and **2a–d**) as oils. The following products were thus prepared:

#### *N,N*-Bis(diethoxyphosphinoylmethyl)glycine

*Methyl Ester (1b)*. Yield: 85% (0.56 g); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ: 23.8; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 16.4 (d, <sup>3</sup>J<sub>CP</sub> = 6.1, CH<sub>2</sub>CH<sub>3</sub>), 50.5 (dd, <sup>1</sup>J<sub>CP</sub> = 136.7, <sup>3</sup>J<sub>CP</sub> = 10.2, CH<sub>2</sub>P), 51.8 (OCH<sub>3</sub>), 55.7 (t, <sup>3</sup>J<sub>CP</sub> = 6.0, CH<sub>2</sub>N), 62.1 (d, <sup>2</sup>J<sub>CP</sub> = 7.0, CH<sub>2</sub>CH<sub>3</sub>), 171.0 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.28 (t, <sup>3</sup>J<sub>HH</sub> = 7.0, 12H, CH<sub>2</sub>CH<sub>3</sub>), 3.26 (d, <sup>2</sup>J<sub>PH</sub> = 10.3, 4H, CH<sub>2</sub>P), 3.66 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 2H, CH<sub>2</sub>N), 4.05–4.18 (m, 8H, CH<sub>2</sub>CH<sub>3</sub>); [M + H]<sup>+</sup><sub>found</sub> = 390.1448, C<sub>13</sub>H<sub>30</sub>NO<sub>8</sub>P<sub>2</sub> requires 390.1447.

#### *N,N*-Bis(dibutoxyphosphinoylmethyl)glycine

*Methyl Ester (1c)*. Yield: 93% (0.79 g); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ: 23.9; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 13.5 (CH<sub>2</sub>CH<sub>3</sub>), 18.7 (CH<sub>2</sub>CH<sub>3</sub>), 32.5 (d, <sup>3</sup>J<sub>CP</sub> = 6.2, OCH<sub>2</sub>CH<sub>2</sub>), 50.5 (dd, <sup>1</sup>J<sub>CP</sub> = 160.2, <sup>3</sup>J<sub>CP</sub> = 10.1, CH<sub>2</sub>P), 51.3 (OCH<sub>3</sub>), 55.6 (t, <sup>3</sup>J<sub>CP</sub> = 5.8, CH<sub>2</sub>N), 65.8 (d, <sup>2</sup>J<sub>CP</sub> = 7.2, OCH<sub>2</sub>), 171.0 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.90 (t, <sup>3</sup>J<sub>HH</sub> = 7.4, 12H, CH<sub>2</sub>CH<sub>3</sub>), 1.29–1.44 (m, 8H, CH<sub>2</sub>CH<sub>3</sub>), 1.55–1.68 (m, 8H, OCH<sub>2</sub>CH<sub>2</sub>), 3.27 (d, <sup>2</sup>J<sub>PH</sub> = 10.2, 4H, CH<sub>2</sub>P), 3.66 (s, 3H, OCH<sub>3</sub>), 3.79 (s, 2H, CH<sub>2</sub>N), 3.99–4.11 (m, 8H, OCH<sub>2</sub>); [M + H]<sup>+</sup><sub>found</sub> = 502.2708, C<sub>21</sub>H<sub>46</sub>NO<sub>8</sub>P<sub>2</sub> requires 502.2699.

#### *N,N*-Bis(dimethoxyphosphinoylmethyl)glycine

*Ethyl Ester (2a)*. Yield: 70% (0.41 g); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ: 26.1; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 14.1 (OCH<sub>2</sub>CH<sub>3</sub>), 49.8 (dd, <sup>1</sup>J<sub>CP</sub> = 161.7, <sup>3</sup>J<sub>CP</sub> = 9.8, CH<sub>2</sub>P), 52.8 (d, <sup>2</sup>J<sub>CP</sub> = 7.0, OCH<sub>3</sub>), 56.0 (t, <sup>3</sup>J<sub>CP</sub> = 6.4, CH<sub>2</sub>N), 60.5 (OCH<sub>2</sub>CH<sub>3</sub>), 170.4 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.24 (t, <sup>3</sup>J<sub>HH</sub> = 7.1, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 3.29 (d, <sup>2</sup>J<sub>PH</sub> = 10.3, 4H, CH<sub>2</sub>P), 3.75 (s, 12H, OCH<sub>3</sub>), 3.79 (s, 2H, CH<sub>2</sub>N), 4.09–4.19 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>); [M + H]<sup>+</sup><sub>found</sub> = 348.0973, C<sub>10</sub>H<sub>24</sub>NO<sub>8</sub>P<sub>2</sub> requires 348.0977.

#### *N,N*-Bis(diethoxyphosphinoylmethyl)glycine

*Ethyl Ester (2b)*. Yield: 85% (0.56 g); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ: 23.8; δ [35] (CDCl<sub>3</sub>) 23.4; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 14.1 (OCH<sub>2</sub>CH<sub>3</sub>), 16.4 (d, <sup>3</sup>J<sub>CP</sub> = 6.1, CH<sub>2</sub>CH<sub>3</sub>), 50.5 (dd, <sup>1</sup>J<sub>CP</sub> = 136.7, <sup>3</sup>J<sub>CP</sub> = 10.2, CH<sub>2</sub>P), 51.8 (OCH<sub>3</sub>), 55.7 (t, <sup>3</sup>J<sub>CP</sub> = 6.0, CH<sub>2</sub>N), 62.1 (d, <sup>2</sup>J<sub>CP</sub> = 7.0, CH<sub>2</sub>CH<sub>3</sub>), 171.0 (C=O); δ [35]\* (CDCl<sub>3</sub>) 51.09 (dd, <sup>1</sup>J<sub>CP</sub> = 159.9, <sup>3</sup>J<sub>CP</sub> = 10.6, CH<sub>2</sub>P), 56.17 (t, <sup>3</sup>J<sub>CP</sub> = 6.7, CH<sub>2</sub>N), 170.49 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.28 (t, <sup>3</sup>J<sub>HH</sub> = 7.0, 12H, CH<sub>2</sub>CH<sub>3</sub>), 3.26 (d, <sup>2</sup>J<sub>PH</sub> = 10.3, 4H, CH<sub>2</sub>P), 3.66 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 2H, CH<sub>2</sub>N), 4.05–4.18 (m, 8H, CH<sub>2</sub>CH<sub>3</sub>); δ [35]\* (CDCl<sub>3</sub>) 3.45 (d, <sup>2</sup>J<sub>PH</sub> = 9.5, 4H, CH<sub>2</sub>P), 4.01 (s, 2H, CH<sub>2</sub>N), \*Signals of ethyl group are missing; [M + H]<sup>+</sup><sub>found</sub> = 404.1605, C<sub>14</sub>H<sub>32</sub>NO<sub>8</sub>P<sub>2</sub> requires 404.1603.

#### *N,N*-Bis(dibutoxyphosphinoylmethyl)glycine

*Ethyl Ester (2c)*. Yield: 93% (0.79 g); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ: 23.9; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 13.5 (CH<sub>2</sub>CH<sub>3</sub>), 14.1 (OCH<sub>2</sub>CH<sub>3</sub>), 18.7 (CH<sub>2</sub>CH<sub>3</sub>), 32.5 (d, <sup>3</sup>J<sub>CP</sub> = 6.2, OCH<sub>2</sub>CH<sub>2</sub>), 50.5 (dd, <sup>1</sup>J<sub>CP</sub> = 160.2, <sup>3</sup>J<sub>CP</sub> = 10.1, CH<sub>2</sub>P), 51.3 (OCH<sub>3</sub>), 55.6 (t, <sup>3</sup>J<sub>CP</sub> = 5.8, CH<sub>2</sub>N), 65.8 (d, <sup>2</sup>J<sub>CP</sub> = 7.2, OCH<sub>2</sub>), 171.0 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.90 (t, <sup>3</sup>J<sub>HH</sub> = 7.4, 12H, CH<sub>2</sub>CH<sub>3</sub>), 1.29–1.44 (m, 8H, CH<sub>2</sub>CH<sub>3</sub>), 1.55–1.68 (m, 8H, OCH<sub>2</sub>CH<sub>2</sub>), 3.27 (d, <sup>2</sup>J<sub>PH</sub> = 10.2, 4H, CH<sub>2</sub>P), 3.66 (s, 3H, OCH<sub>3</sub>), 3.79 (s, 2H, CH<sub>2</sub>N), 3.99–4.11 (m, 8H, OCH<sub>2</sub>); [M + H]<sup>+</sup><sub>found</sub> = 516.2855, C<sub>22</sub>H<sub>48</sub>NO<sub>8</sub>P<sub>2</sub> requires 516.2855.

#### *N,N*-Bis(dibenzilyoxyphosphinoylmethyl)glycine

*Ethyl Ester (2d)*. Yield: 96% (1.06 g); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ: 26.1; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 14.1 (OCH<sub>2</sub>CH<sub>3</sub>), 49.8 (dd, <sup>1</sup>J<sub>CP</sub> = 161.7, <sup>3</sup>J<sub>CP</sub> = 9.8, CH<sub>2</sub>P), 52.8 (d, <sup>2</sup>J<sub>CP</sub> = 7.0, OCH<sub>3</sub>), 56.0 (t, <sup>3</sup>J<sub>CP</sub> = 6.4, CH<sub>2</sub>N), 60.5 (OCH<sub>2</sub>CH<sub>3</sub>), 170.4 (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.24 (t, <sup>3</sup>J<sub>HH</sub> = 7.1, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 3.29 (d, <sup>2</sup>J<sub>PH</sub> = 10.3, 4H, CH<sub>2</sub>P), 3.75 (s, 12H, OCH<sub>3</sub>), 3.79 (s, 2H, CH<sub>2</sub>N), 4.09–4.19 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>);

$[M + H]^+$  found = 652.2239,  $C_{34}H_{40}NO_8P_2$  requires 652.2229.

*N*-(Diethoxyphosphinoylmethyl)glycine ethyl ester (**5**) was prepared as bisadduct **2b**, but the three reactants were used in an equimolar quantity. Yield after flash column chromatography: 73%.  $^{31}P$  NMR ( $CDCl_3$ )  $\delta$ : 23.6;  $\delta[32]$  ( $CDCl_3$ ) 22.9;  $[M + H]^+$  found = 254.1162,  $C_9H_{21}NO_5P$  requires 254.1157.

#### General procedure for the synthesis of *N,N*-bis(diphenylphosphinoylmethyl)glycine esters

A mixture of 0.85 mmol glycine ester (0.08 g of glycine ethyl ester or 0.09 g of glycine methyl ester), 0.05 g (1.70 mmol) of paraformaldehyde, and 0.34 g (1.70 mmol) of diphenylphosphine oxide in 3 mL of acetonitrile was heated at 100°C in a closed vial in the MW reactor for 1 h. The workup was similar as above to provide products **3** and **4** as oils.

*N,N*-Bis(diphenylphosphinoylmethyl)glycine Methyl Ester (**3**). Yield: 92% (0.40 g);  $^{31}P$  NMR ( $CDCl_3$ )  $\delta$ : 29.7;  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$ : 51.4 ( $OCH_3$ ), 55.2 (dd,  $^1J_{CP} = 84.4$ ,  $^3J_{CP} = 7.7$ ,  $CH_2P$ ), 57.6 (t,  $^3J_{CP} = 6.2$ ,  $CH_2N$ ), 128.4 (d,  $J_{CP} = 11.7$ ,  $C_2$ ),\* 131.1 (d,  $J_{CP} = 9.3$ ,  $C_3$ ),\* 131.6 (d,  $^1J_{CP} = 98.6$ ,  $C_1$ ), 131.7 (d,  $^4J_{CP} = 2.7$ ,  $C_4$ ), \*may be reversed;  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 3.04 (s, 4H,  $CH_2P$ ), 3.65 (s, 3H,  $OCH_3$ ), 3.95 (s, 2H,  $CH_2N$ ), 7.28–7.53 (m, 12H, ArH), 7.63–7.79 (m, 8H, ArH);  $[M + H]^+$  found = 518.1650,  $C_{29}H_{30}NO_4P_2$  requires 518.1650.

*N,N*-Bis(diphenylphosphinoylmethyl)glycine Ethyl Ester (**4**). Yield: 88% (0.40 g);  $^{31}P$  NMR ( $CDCl_3$ )  $\delta$ : 29.8;  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$ : 14.1 ( $CH_3$ ), 55.2 (dd,  $^1J_{CP} = 84.3$ ,  $^3J_{CP} = 7.4$ ,  $CH_2P$ ), 57.8 (t,  $^3J_{CP} = 6.7$ ,  $CH_2N$ ), 60.4 ( $OCH_2$ ), 128.4 (d,  $J_{CP} = 11.7$ ,  $C_2$ ),\* 131.1 (d,  $J_{CP} = 9.3$ ,  $C_3$ ),\* 131.6 (d,  $^1J_{CP} = 98.4$ ,  $C_1$ ), 131.7 (d,  $^4J_{CP} = 2.7$ ,  $C_4$ ), \*may be reversed;  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 1.21 (t,  $^3J_{HH} = 7.1$ , 3H,  $OCH_2CH_3$ ), 3.45–3.61 (m, 4H,  $CH_2P$ ), 3.94 (s, 2H,  $CH_2N$ ), 4.06–4.15 (m, 2H,  $OCH_2$ ), 7.29–7.54 (m, 12H, ArH), 7.65–7.83 (m, 8H, ArH);  $[M + H]^+$  found = 532.1808,  $C_{30}H_{32}NO_4P_2$  requires 532.1807.

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