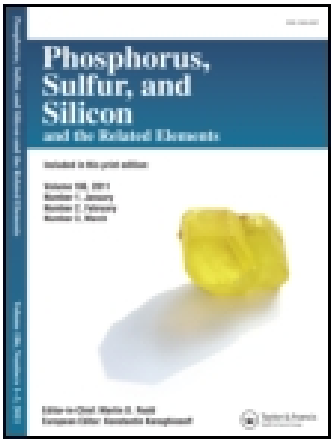

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Comparative Studies on the Amidoalkylating Properties of N-(1-Methoxyalkyl)Amides and 1-(N-Acylamino)Alkyltriphenylphosphonium Salts in the Michaelis-Arbuzov-Like Reaction: A New One-Pot Transformation of N-(1-Methoxyalkyl)Amides into Phosphonic or Phosphinic Analogs of N-Acyl-α-Amino Acids

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Accepted author version posted online: 05 Oct 2012.Published online: 05 Jul 2013.

To cite this article: Jakub Adamek, Agnieszka Październiok-Holewa, Katarzyna Zielińska & Roman Mazurkiewicz (2013) Comparative Studies on the Amidoalkylating Properties of N-(1-Methoxyalkyl)Amides and 1-(N-Acylamino)Alkyltriphenylphosphonium Salts in the Michaelis-Arbuzov-Like Reaction: A New One-Pot Transformation of N-(1-Methoxyalkyl)Amides into Phosphonic or Phosphinic Analogs of N-Acyl-α-Amino Acids, Phosphorus, Sulfur, and Silicon and the Related Elements, 188:7, 967-980, DOI: 10.1080/10426507.2012.729237

To link to this article: http://dx.doi.org/10.1080/10426507.2012.729237

Phosphorus, Sulfur, and Silicon, 188:967–980, 2013

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.729237

COMPARATIVE STUDIES ON THE AMIDOALKYLATING PROPERTIES OF *N*-(1-METHOXYALKYL)AMIDES AND 1-(*N*-ACYLAMINO)ALKYLTRIPHENYLPHOSPHONIUM SALTS IN THE MICHAELIS–ARBUZOV-LIKE REACTION: A NEW ONE-POT TRANSFORMATION OF *N*-(1-METHOXYALKYL)AMIDES INTO PHOSPHONIC OR PHOSPHINIC ANALOGS OF *N*-ACYL-α-AMINO ACIDS

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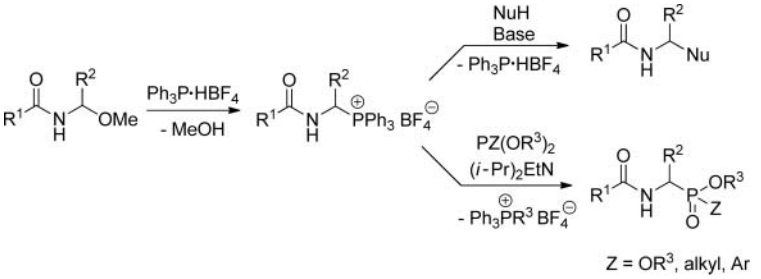
GRAPHICAL ABSTRACT



Abstract *It was demonstrated that N-(1-methoxyalkyl)amides do not react with trimethyl phosphite under neutral or basic conditions. The treatment of N-(1-methoxyalkyl)amides with trialkyl phosphites or dialkyl phosphonites, triphenylphosphonium tetrafluoroborate, and Hünig's base caused immediate formation of the corresponding 1-(N-acylamino)-alkyltriphenylphosphonium tetrafluoroborates, followed by the slow Michaelis–Arbuzov-like reaction of phosphonium salt with phosphites or phosphonites to α-(N-acylamino)-alkanephosphonic or α-(N-acylamino)alkanephosphinic acid esters, respectively. A plausible mechanism of the considered transformations, assuming an equilibrium between N-(1-alkoxyalkyl)amide, triphenylphosphonium tetrafluoroborate, 1-(N-acylamino)alkyltriphenyl-phosphonium salt, N-acylimine, and N-acyliminium salts, is discussed.*

Keywords Amidoalkylating agents; 1-(*N*-acylamino)alkyltriphenylphosphonium salts; *N*-(1-methoxyalkyl)amides; Michaelis–Arbuzov-like reaction; phosphorus analogs of *N*-acyl-α-amino acids

Received 12 August 2012; accepted 7 September 2012.

The financial help of the Ministry of Science and Higher Education of Poland (Grant No. N N204 165636) is gratefully acknowledged.

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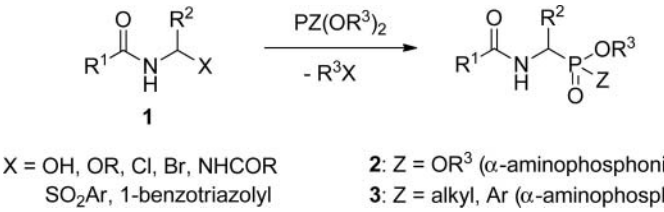
INTRODUCTION

α-Aminoalkanephosphonic acids **2** and α-aminoalkanephosphinic acids **3**, as structural analogues and mimetics of α-amino acids, display a broad spectrum of biological activity and, therefore, have been the subject of significant current interest.[1–3] One of the most general and widely used methods for the synthesis of these compounds consists in the amidoalkylation of trialkyl phosphites or dialkyl phosphonites, respectively, in a Michaelis–Arbuzov-like reaction (Scheme 1).[4]

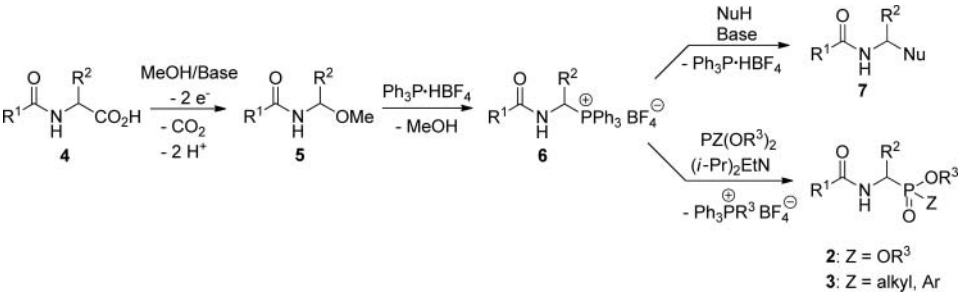


Scheme 1

Numerous α-amidoalkylating reagents of a general structure **1** have been used in those reactions, where X represents some nucleofugal leaving group, usually OH, OR, Cl, Br, NHCOR, SO_2Ar, or 1-benzotriazolyl (Scheme 1).[4–13]

The limitations and disadvantages of most of the above-mentioned amidoalkylating agents were reviewed by Katritzky et al.[4,14–17] Many of them (X = OR, Cl, Br) are relatively unstable compounds that cannot be stored for a prolonged period of time and thus have to be prepared in situ. Preparation of some of these amidoalkylating agents (X = Cl, Br) is relatively difficult or labor-consuming. Most of them (X = OH, NHCOR, or 1-benzotriazolyl), including the most frequently used α-alkoxy derivatives (X = OR), require activation with Lewis acids, which are often quite expensive (e.g., $ZrCl_4$, VCl_3, $CeCl_3$, or $InCl_3$).[4,13–17] Application of Lewis acid has also been shown to diminish the activity of a reacting nucleophile and also necessitates a labor-consuming aqueous work-up procedure, which usually destroys the catalyst.

N-(1-Alkoxyalkyl)amides **5** represent an especially interesting class of amidoalkylating agents, as they can be obtained directly from easily accessible *N*-acyl-α-amino acids **4** by electrochemical decarboxylative α-alkoxylation (usually α-methoxylation), well known as the Hofer–Moest reaction (Scheme 2; transformation **4** to **5**).[18–30] *N*-(1-Alkoxyalkyl)amides



Scheme 2

5 can also be obtained by electrochemical oxidation of *N*-alkylamides, lactams, and *N*-alkylcarbamates in methanol.[23,31,32] Recently, we described an effective and convenient procedure for the Hofer–Moest decarboxylative α-methoxylation of a variety of *N*-acyl-α-amino acids in the presence of silica gel-supported piperidine as a base.[33] The possibility of employing a large variety of natural α-amino acids (both proteinogenic and unproteinogenic) in this synthesis, as well as a nearly infinite array of unnatural α-amino acids both provide potential access to a wide variety of structurally diverse *N*-(1-alkoxyalkyl)amides, which significantly broadens the scope of possible synthetic application of their amidoalkylating properties.

N-(1-Alkoxyalkyl)amides are also promising intermediates for a relatively straightforward two-stage transformation of *N*-acyl-α-amino acids into their phosphonic or phosphinic analogs. In 1981, Shono et al. reported the Michaelis–Arbuzov-like reaction of *N*-(1-methoxyalkyl)amides with trialkyl or triphenyl phosphites in the presence of Lewis acids ($TiCl_4$, $ZnCl_2$, $SnCl_4$, or $BF_3{\cdot}OEt_2$) to the corresponding α-aminoalkylphosphonic acid derivatives.[9] About 10 years later Seebach and Gerber described the decarboxylative α-methoxylation of the *C*-terminal amino acid of dipeptides followed by the reaction of α-methoxy derivatives with trialkyl or triaryl phosphites in the presence of $TiCl_4$ to the corresponding phosphonodipeptide derivatives, which were usually obtained in moderate to good yields based on the dipeptide.[34,35]

Recently, we reported on a very simple and efficient transformation of *N*-(1-methoxyalkyl)amides **5** to the hitherto unknown 1-(*N*-acylamino)alkyltriphenylphosphonium salts **6** (Scheme 2).[33,36,37] We also demonstrated that the phosphonium salts **6** display strong amidoalkylating properties when activated with organic bases. They react smoothly with oxygen, nitrogen, sulphur, and carbon nucleophiles in the presence of $(i\text{-Pr})_2EtN$ (Hünig's base) or DBU to give α-amidoalkylation products **7**.[36] Moreover, α-amidoalkylation of trialkyl phosphites or dialkyl phosphonites with 1-(*N*-acylamino)alkyltriphenylphosphonium salts, followed by a Michaelis–Arbuzov-like rearrangement, enabled us to perform an effective three-stage transformation of *N*-acyl-α-amino acids **4** to their phosphonic or phosphinic analogs **2** or **3**, respectively (Scheme 2).

In the present paper, we report our comparative and mechanistic study on the amidoalkylation properties of *N*-(1-methoxyalkyl)amides **5** and 1-(*N*-acylamino)alkyltriphenylphosphonium salts **6** in the Michaelis–Arbuzov-like reaction with trialkyl phosphites, as well as investigations on the mechanism of the transformation of *N*-(1-methoxyalkyl)amides **5** to phosphonium salts **6**. These investigations have allowed us to simplify the above-mentioned three-stage transformation of *N*-acylamino acids **4** into their phosphorus analogues **2** or **3** to a simple two-stage method which does not use Lewis acids.

RESULTS AND DISCUSSION

The mechanism of the Michaelis–Arbuzov-like reaction of *N*-(1-methoxyalkyl)amides **5** and 1-(*N*-acylamino)alkyltriphenylphosphonium salts **6** was studied based mainly on the reaction of *N*-(1-methoxyethyl)pivaloamide **5a** and the corresponding 1-(*N*-pivaloylamino)ethyltriphenylphosphonium tetrafluoroborate **6a** with trialkyl phosphites.

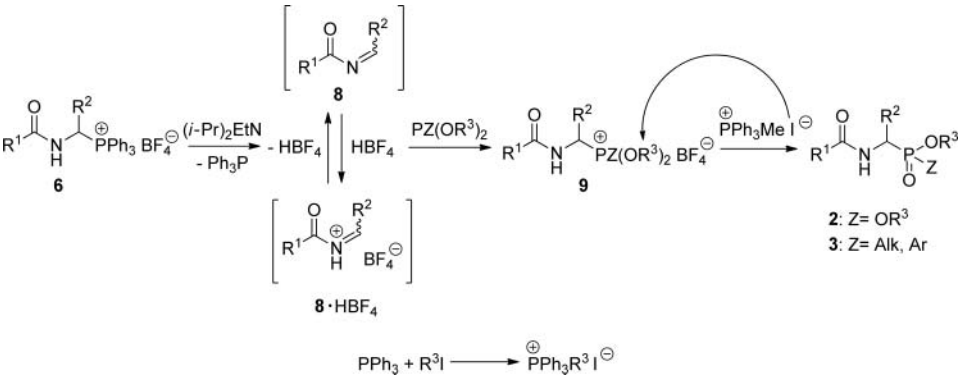
The reaction of phosphonium salt **6a** with trimethyl phosphite in CD_2Cl_2 at 20 °C was very slow; after 157 min the reaction mixture contained only about 13% of the expected aminophosphonic acid derivative **2**, apart from the starting reagents (Table 1, entry 1).

Table 1 1-(*N*-Acylamino)alkyltriphenylphosphonium salts **6** and *N*-(1-methoxyalkyl)amides **5** in the synthesis of α-(*N*-acylamino)alkanephosphonic **2** and α-(*N*-acylamino)alkanephosphinic acid esters **3**

Entry	Substrate **5** or **6**			Nucleophile	Molar ratio of **5** (or **6**): Nucleophile:$Ph_3P{\cdot}HBF_4$: $(i\text{-Pr})_2EtN$:$Ph_3PMe^{\oplus}I^{\ominus}$	Temperature [°C]	Time [min]	Yield of **2** or **3** [%]		
		R^1	R^2					No	Estimated[a]	Isolated
1	**6a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:0:0:0	20	157	**2a**	13	—
2	**6a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:0:0.1:0	20	146	**2a**	67	—
3	**6a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:0:0.1:0	20	3860	**2a**	97	—
4	**6a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:0:0.1:0.25	20	143	**2a**	71	—
5	**6a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:0:0.1:0.25	20	266	**2a**	77	—
6	**6a**	*t*-Bu	Me	$P(OEt)_3$	1:1.5:0:0.1:0	20	180	**2b**	73	—
7	**6b**	BnO	Me	$P(OMe)_3$	1:1.5:0:0.1:0	20	180	**2c**	100	—
8	**6c**	BnO	Bn	$P(OMe)_3$	1:1.5:0:0.1:0	20	160	**2d**	10	—
9	**6c**	BnO	Bn	$P(OMe)_3$	1:1.5:0:0.1:0.25	20	152	**2d**	49	—
10	**6c**	BnO	Bn	$P(OMe)_3$	1:1.5:0:0.1:0.25	20	1060	**2d**	64	—
11	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:0:0:0	20	158	**2a**	0	—
12	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:0:0.1:0	20	157	**2a**	0	—
13	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:0:0:0.25	20	153	**2a**	0	—
14	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:1:0.1:0	20	182	**2a**	18	—
15	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:1:0.1:0	20	4820	**2a**	80	—
16	**5a**	*t*-Bu	Me	$P(OEt)_3$	1:1.5:1:0.1:0	20	124	**2b**	17	—
17	**5a**	*t*-Bu	Me	$P(OEt)_3$	1:1.5:1:0.1:0	20	4790	**2b**	85	—
18	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:1:0.1:0.25	20	180	**2a**	37	—
19	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:1:0.1:0.25	20	1670	**2a**	46	—
20	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:1:0.1:0.25	60	45	**2a**	48	—
21	**5a**	*t*-Bu	Me	$P(OEt)_3$	1:1.5:1:0.1:0.25	60	120	**2b**	91	—
22	**5a**	*t*-Bu	Me	$P(OMe)_3$	1:1.5:1:0.1:0	60	120	**2a**	89	88
23	**5a**	*t*-Bu	Me	$PPh(OEt)_2$	1:1.5:1:0.1:0	60	120	**3a**	78	68
24	**5a**	*t*-Bu	Me	$PEt(OEt)_2$	1:1.5:1:0.1:0	60	120	**3b**	83	68
25	**5b**	BnO	Me	$P(OMe)_3$	1:1.5:1:0.1:0	60	120	**2c**	90	70
26	**5c**	BnO	Bn	$P(OEt)_3$	1:1.5:1:0.1:0.25	60	120	**2e**	90	76
27	**5d**	BnO	CH_2O-*t*-Bu	$PPh(OEt)_2$	1:1.5:1:0.1:0.25	60	120	**3c**	84	67
28	**5e**	BnO	Ph	$P(OEt)_3$	1:1.5:1:0.1:0.25	60	120	**2f**	88	81

[a]Based on ^1H NMR spectra.

The addition of a substoichiometric amount of Hünig's base (0.1 mol per 1 mol of phosphonium salt) significantly speeded up the reaction. After 146 min, the reaction mixture contained 67% of the expected product, 32% of the starting phosphonium salt, 43% of trimethyl phosphite, 10% of triphenylphosphine, and 63% of methyltriphenylphosphonium tetrafluoroborate, whereas after 65 h a 97% yield of the product was achieved (entries 2 and 3). It seems to be clear that the catalytic effect of Hünig's base in the investigated Michaelis–Arbuzov-like reaction consists in deprotonation of the nitrogen atom of phosphonium salt, which initiates the cleavage of the C–P bond, elimination of triphenylphosphine and the formation of *N*-acylimine **8** in equilibrium with *N*-acyliminium salt **8** · HBF_4 as the active amidoalkylating agents (Scheme 3). The reaction of *N*-acylimine or *N*-acyliminium salt with trimethyl phosphite gives trialkoxyphosphonium salt **9**, which is a characteristic intermediate of the Michaelis–Arbuzov reaction. The final step of the ordinary Michaelis–Arbuzov reaction consists in dealkylation of the trialkoxyphosphonium salt with a halogen counterion. It is evident that, in the discussed experiments, trialkoxyphosphonium tetrafluoroborate is dealkylated directly by triphenylphosphine with the formation of methyltriphenylphosphonium tetrafluoroborate and the expected aminophosphonic acid derivative **2**.



Scheme 3

The approach of the bulky triphenylphosphine molecule to the α-atom of the alkoxy group in an S_N2 reaction can be hindered by steric reasons. To avoid this problem, the addition of substoichiometric amounts of iodide anion in the form of methyltriphenylphosphonium iodide as dealkylating agent was tested. A comparison of the results of experiments 2 and 4 led to the conclusion that in the case of phosphonium salts with a relatively small methyl group at the α-position, the addition of methyltriphenylphosphonium iodide did not markedly accelerate the reaction. This means that, in such a case, triphenylphosphine can effectively dealkylate the trialkoxyphosphonium salt even in the case of phosphonium salts **6** with a bulky acyl group or a reaction with triethyl phosphite (entries 6 and 7). On the other hand, in the case of more sterically hindered phosphonium salts with a bulky substituent at the α-position, for example, derived from Cbz–Phe–OH **6c** (entry 8), the Michaelis–Arbuzov reaction without the addition of methyltriphenylphosphonium iodide was slow. After 160 min the conversion of the phosphonium salt into the corresponding aminophosphonic acid derivative reached only 10% at 20 °C. The same phosphonium salt **6c** in the presence of methyltriphenylphosphonium iodide, used in a molar ratio of

1:0.25, was converted into the expected product in 49% after 152 min, whereas after 18 h the reaction mixture contained 64% of the product and 1.06 mol of methyltriphenylphosphonium salt per 1 mol of the starting phosphonium salt **6c** (entries 9-10). This proves that methyl iodide, formed in the demethylation reaction, reacts with triphenylphosphine to methyltriphenylphosphonium iodide, and thus restores the iodide anion which, therefore, can be considered as a real nucleophilic catalyst of the considered reaction (Scheme 3, $R^3 = Me$).

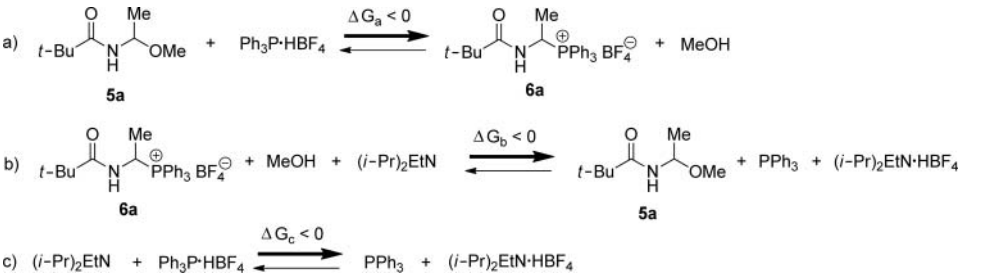
As was expected, the corresponding *N*-(1-methoxyethyl)pivaloamide **5a** did not react directly with trimethyl phosphite. The reaction also did not take place in the presence of Hünig's base or methyltriphenylphosphonium iodide (entries 11–13). Therefore, a direct reaction of the *N*-(1-methoxyethyl)pivaloamide with trimethylphosphite in the Michaelis–Arbuzov reaction under neutral or basic conditions is not possible.

Attempting to find the conditions for a "one-pot" reaction of *N*-(1-methoxyalkyl)-amides **5** with trialkyl phosphites, we studied their transformation to 1-(*N*-acylamino)alkyltriphenylphosphonium salts **6** in detail.

Our first developed method for displacement of the methoxy groups of *N*-(1-methoxyalkyl)amides with the triphenylphosphonium group consisted in heating of a homogeneous mixture of the amide with triphenylphosphonium tetrafluoroborate at 45–70 °C under reduced pressure (0.1–0.2 mm Hg) for 2 h.[33] Our recent investigations revealed, however, that high or even quantitative yields of this transformation could be achieved simply by dissolution of *N*-(1-methoxyalkyl)amide and triphenylphosphonium tetrafluoroborate in CD_2Cl_2 at room temperature for 5 to 15 min and by evaporation of the solvent.[33] The reaction was so fast that it was not possible to monitor the reaction progress in the range of low or medium conversions by ^1H NMR spectroscopy.[33]

Developing these studies, we found that the addition of an equimolar amount of Hünig's base to a mixture of 1-(*N*-pivaloylamino)ethyltriphenylphosphonium tetrafluoroborate **6a** and methanol in CD_2Cl_2, obtained *in situ* from *N*-(1-methoxyethyl)pivaloamide **5a** and triphenylphosphonium tetrafluoroborate, initiated unexpectedly a slow reverse reaction. After 60 min, the reaction mixture contained 23% of the methoxy derivative **5a**, 57% of the phosphonium salt **6a**, and 22% of the enamide **10a**, whereas after 80 h, the mixture contained about 60% of the *N*-(1-methoxyethyl)pivaloamide **5a**, 35% of enamide **10a**, and a trace amount of the phosphonium salts **6a**. We obtained almost the same result by starting from a solution of equimolar amounts of 1-(*N*-pivaloylamino)ethyltriphenylphosphonium tetrafluoroborate **6a**, methanol and Hünig's base in CD_2Cl_2: after 60 min the reaction mixture contained 18% of the methoxy derivative **5a**, 57% of the phosphonium salt **6a** and 18% of the enamide **10a**. When only 0.1 mol of Hünig's base per 1 mol of phosphonium salt **6a** and 1 mol of methanol were used, the reverse reaction stopped at about 10% of conversion to *N*-(1-methoxyethyl)pivaloamide **5a**. These results prove that the investigated displacement of the methoxy group of *N*-(1-methoxyalkyl)amides with triphenylphosphine is a reversible reaction.

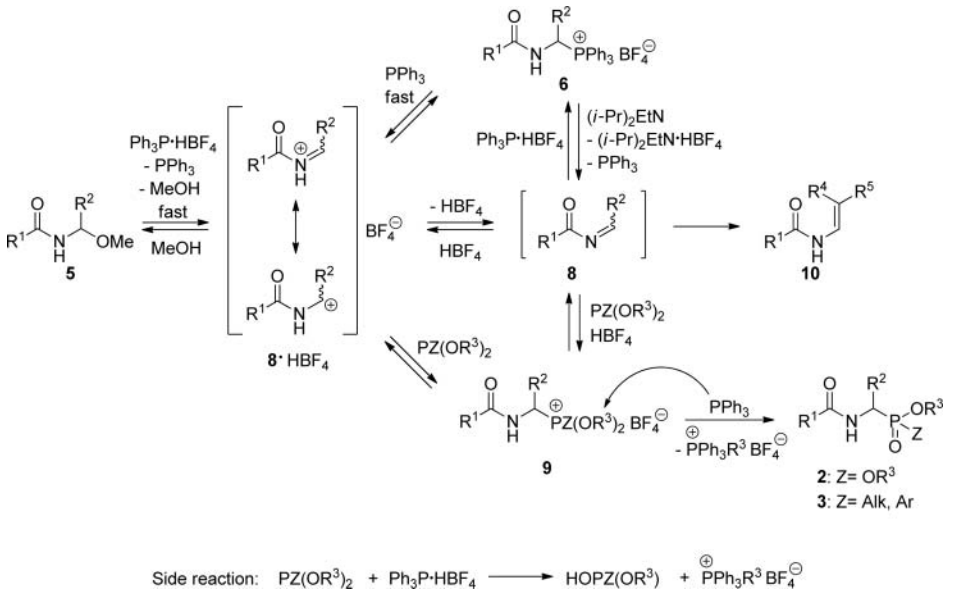
The nature of the driving force of the discussed reverse displacement of the phosphonium group with methanol (Scheme 4, reaction "b") can be explained by taking into account that the summing up of the first two equations in Scheme 4 gives the third equation. This means that the relations between the free energies of these reactions are as follows: $\Delta G_a + \Delta G_b = \Delta G_c$, and consequently $\Delta G_b = \Delta G_c - \Delta G_a$. The free energy of the third reaction is evidently negative; the reaction of Hünig's base with triphenylphosphonium tetrafluoroborate in CD_2Cl_2 immediately gave a mixture of free triphenylphosphine and Hünig's base salt. This analysis indicates that the negative value of free energy of reaction



Scheme 4

"b" ($\Delta G_b < 0$), which is necessary for the spontaneous course of this reaction, is achieved, because the free energy of reaction "c" is more negative than the free energy of reaction "a" ($\Delta G_c < \Delta G_a$). Therefore, a high negative value of free energy of the formation of the Hünig's base salt in reaction "c" must be responsible for a negative value of ΔG_b and, consequently, is the driving force of the reverse displacement of the phosphonium group with methanol in the presence of Hünig's base.

Assuming that the equilibrium between *N*-(1-alkoxyalkyl)amides **5** and 1-(*N*-acylamino)alkyltriphenylphosphonium salts **6** is achieved *via* *N*-acylimines **8** or *N*-acyliminium salts **8** · HBF_4 (Scheme 5), we tried to find favorable conditions for a direct Michaelis–Arbuzov-like reaction of *N*-(1-methoxyethyl)pivaloamide **5a** with trimethylphosphite in the presence of triphenylphosphonium tetrafluoroborate and Hünig's base. As was expected, *N*-(1-methoxyethyl)pivaloamide **5a** was immediately transformed to the corresponding phosphonium salt **6a** at the molar ratio of the reagents of 1:1.5:1.0:0.1, respectively, in CD_2Cl_2 at 20 °C in a yield of about 99%. However, after 182 min, the



Scheme 5

reaction mixture contained 18% of the expected α-aminoethanephosphonic acid derivative **2a**, and after about 80 h, the reaction system approached equilibrium with a yield of **2a** at a level of 80% (Table 1, entries 14–15). The final reaction mixture also contained the starting *N*-(1-methoxyethyl)amide **5a** (11%), phosphonium salt **6a** (10%), methanol (63%), triphenylphosphine (11%), methyltriphenylphosphonium tetrafluoroborate (82%), starting trimethylphosphite (28%), and, unexpectedly, dimethylphosphite (10%). Very similar results were obtained in a reaction of amide **5a** with triethylphosphite (entries 16–17).

A plausible mechanism of the considered transformations, assuming an equilibrium between *N*-(1-alkoxyalkyl)amide **5**, triphenylphosphonium tetrafluoroborate, 1-(*N*-acylamino)alkyltriphenylphosphonium salt **6**, *N*-acylimine **8**, and *N*-acyliminium salts **8** · HBF_4, is shown in Scheme 5.

It seems that the mechanism of transforming *N*-(1-methoxyalkyl)amides **5** to triphenylphosphonium tetrafluoroborates **6** consists in the protonation of the methoxy group, followed by the elimination of methanol with formation of the acyliminium salt **8** · HBF_4 in equilibrium with the acylimine **8**. The α-amidoalkylation of trimethylphosphite with **8** · HBF_4 or **8** finally gave the expected Michaelis–Arbuzov reaction product **2** or **3**, as was discussed above.

The final yield of the Michaelis–Arbuzov-like reaction of amide **5a** with trimethylphosphite (entry 15) was fairly good (80%); however, the reaction was relatively slow. Adding 0.25 mol of methyltriphenylphosphonium iodide per 1 mol of amide **5a** to the reaction mixture distinctly speeded up the reaction (entry 18); however, the final reaction yield was worse (46%, entry 19) due to the intensive demethylation of trimethyl phosphite with triphenylphosphonium tetrafluoroborate to dimethyl phosphite, which was evidently catalyzed by methyltriphenylphosphonium iodide (Scheme 5). Raising the reaction temperature to 60 °C speeded up the reaction; however, the reaction yield did not exceed 50% (entry 20). Finally, we demonstrated that using triethyl phosphite instead of trimethyl phosphite significantly decreased the amount of the undesired phosphite's dealkylation and allowed to obtain a good final reaction yield (entry 21).

The aforementioned observations enabled us to elaborate an effective one-pot procedure for the synthesis of α-(*N*-acylamino)alkanephosphonic or α-(*N*-acylamino)alkanephosphinic acid esters directly from *N*-(1-methoxyalkyl)amides **5** and trialkyl phosphites or dialkyl phosphonites, respectively, without the use of Lewis acids. For *N*-(1-methoxyethyl)-amides **5a**,**b** with a small methyl group at the α-position (Table 1, entries 22–25) heating of these reagents in CH_2Cl_2 in the presence of triphenylphosphonium tetrafluoroborate and Hünig's base in a molar ratio of 1:1.5:1:0.1, respectively, at 60 °C for 2 h, without the use of methyltriphenylphosphonium iodide, gave the expected products in good yields. For amides **5c**–**e** with a bulky alkyl or aryl substituent at the α-position (entries 26–28) the use of methyltriphenylphosphonium iodide as the catalyst of the Michaelis–Arbuzov reaction was necessary. In consequence, in these cases triethylphosphite or diethylphosphonite must be used to avoid dealkylation of the phosphorus nucleophile. A simple work-up procedure of the reaction mixtures, using no water, is a special advantage of this method.

CONCLUSIONS

The Michaelis–Arbuzov-like reaction of 1-(*N*-acylamino)alkyltriphenylphosphonium tetrafluoroborates **6** with trimethyl phosphite to α-(*N*-acylamino)alkanephosphonic acid

esters needed the presence of a basic catalyst (Hünig's base). The trimethoxyphosphonium salt, which is a characteristic intermediate of the Michaelis–Arbuzov reaction, can be demethylated directly by triphenylphosphine to give the expected α-aminoalkanephosphonic acid derivatives. For more sterically hindered phosphonium salts **6**, demethylation of the trimethoxyphosphonium salt could be speeded up by iodide anion as a nucleophilic catalyst introduced with a methyltriphenylphosphonium iodide. It was demonstrated that a direct reaction of the *N*-(1-methoxyalkyl)amides with trimethyl phosphite to α-(*N*-acylamino)alkanephosphonic acid esters under neutral or basic conditions is not possible. Dissolution of *N*-(1-methoxyalkyl)amide and triphenylphosphonium tetrafluoroborate in CD_2Cl_2 at room temperature caused the immediate formation of 1-(*N*-acylamino)alkyltriphenylphosphonium tetrafluoroborates in high yields. The addition of an equimolar amount of Hünig's base to this reaction mixture initiated a slow reverse reaction. These observations made it possible to elaborate the effective one-pot procedure for the synthesis of α-(*N*-acylamino)alkanephosphonic **2** or α-(*N*-acylamino)alkanephosphinic acid esters **3** directly from *N*-(1-methoxyalkyl)amides **5** and trialkyl phosphites or dialkyl phosphonites, respectively, without the use of Lewis acids. The developed method, in connection with the previously elaborated effective procedure for the electrochemical decarboxylative α-methoxylation of *N*-acyl-α-amino acids to *N*-(1-methoxyalkyl)amides,[33] establishes a new, effective, two-stage method for the transformation of *N*-acyl-α-amino acids into their phosphonic or phosphinic analogs. The plausible mechanism of the considered transformations, assuming an equilibrium between *N*-(1-alkoxyalkyl)amide **5**, triphenylphosphonium tetrafluoroborate, 1-(*N*-acylamino)alkyltriphenylphosphonium salt **6**, *N*-acylimine **8**, and *N*-acyliminium salts, was discussed.

EXPERIMENTAL

General Methods

Melting points were determined in capillary tubes with the Stiriling SMP 3 apparatus and are uncorrected. IR spectra were measured with a Nicolett 6700 FTIR spectrophotometer (ATR method). ^{1}H and ^{13}C NMR spectra were recorded with a Varian UNITY INOVA-300 spectrometer at operating frequencies of 300 and 75.5 MHz, respectively, or with an Agilent NMR Magnet 400 MHz spectrometer at operating frequencies of 400 and 100.5 MHz, respectively, using TMS as the resonance shift standard. ^{31}P NMR spectra were recorded with a Varian-600 spectrometer operating at 242.8 MHz, using 80% orthophosphoric acid as the resonance shift standard. All chemical shifts (δ) are reported in ppm, and coupling constants (J) in Hz.

Transformation of *N*-(1-Methoxyalkyl)amides 5 or 1-(*N*-Acylamino)alkyltriphenylphosphonium Salts 6 to α-(*N*-Acylamino)alkanephosphonates 2 (^{1}H NMR Experiments). Reactions were carried out in NMR tubes. To a solution of *N*-(1-methoxyalkyl)amide **5** (0.314 mmol) or 1-(*N*-acylamino)alkyltriphenylphosphonium tetrafluoroborate **6** (0.314 mmol) in CD_2Cl_2 (0.65 mL) trialkyl phosphite (0.471 mmol), triphenylphosphonium tetrafluoroborate, Hünig's base and methyltriphenylphosphonium iodide were added in the molar ratio shown in Table 1. The progress of the reaction was monitored by ^{1}H NMR spectroscopy.

Interaction of *N*-(1-Methoxyethyl)pivaloamide 5a With Triphenylphosphonium Tetrafluoroborate and Hünig's Base (^{1}H NMR Experiment). The reaction was carried out in NMR tube. Triphenylphosphonium tetrafluoroborate (109.9 mg, 0.314 mmol) was added to a solution of *N*-(1-methoxyethyl)pivaloamide **5a** (50.0 mg, 0.314 mmol) in CD_2Cl_2 (0.65 mL). After 10 min. Hünig's base (0.055 mL, 40.6 mg, 0.314 mmol) was added. The progress of the reaction was monitored by ^{1}H NMR spectroscopy before and after adding Hünig's base.

Interaction of 1-(*N*-Pivaloylamino)ethyltriphenylphosphonium Tetrafluoroborate 6a With Methanol and Hünig's Base (^{1}H NMR Experiment). The reaction was carried out in NMR tube. Hünig's base (0.055 mL, 40.6 mg, 0.314 mmol) was added to a solution of 1-(*N*-pivaloylamino)ethyltriphenylphosphonium tetrafluoroborate **6a** (149.9 mg, 0.314 mmol) and methanol (0.013 mL, 10.0 mg, 0.314 mmol) in CD_2Cl_2 (0.65 mL). The progress of the reaction was monitored by ^{1}H NMR spectroscopy.

One-Pot Procedure For the Synthesis of α-(*N*-Acylamino)alkanephosphonates 2 or α-(*N*-Acylamino)alkanephosphinates 3 From *N*-(1-Methoxyalkyl)-amides 5. The reactions were carried out in a glass vial sealed with a screw-cap. Triphenylphosphonium tetrafluoroborate (164.9 mg, 0.471 mmol), trialkyl phosphite, diethyl phenylphosphonite or diethyl ethylphosphonite (0.707 mmol), Hünig's base (6.1 mg, 0.047 mmol), and methyltriphenylphosphonium iodide (47.7 mg, 0.118 mmol) (only in experiments 26–28) were added to a solution of *N*-(1-methoxyalkyl)amide **5** (0.471 mmol) in dichloromethane (1.0 mL). The homogeneous solution was heated at 60 °C for 2 h. The solvent was evaporated under reduced pressure, the residue was extracted with toluene (3 × 1 mL) at 50 °C and the toluene was evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 20:1 v/v or 40:1 v/v).

Dimethyl 1-(*N*-Pivaloylamino)ethanephosphonate (2a)

Colorless crystals, m.p.: 128–129 °C, 98.3 mg, 88%. IR (ATR), ν (cm^{-1}): 3273, 1652, 1527, 1223, 1204, 1057, 1027, 1007. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.16$ (d, $J = 9.0$ Hz, 1H, NH), 4.58 (ddq, $J_1 = 15.6$ Hz, $J_2 = 9.3$ Hz, $J_3 = 7.5$ Hz, 1H, CH), 3.77 (d, $J = 10.5$ Hz, 3H, OCH_3), 3.76 (d, $J = 10.5$ Hz, 3H, OCH_3), 1.39 (dd, $J_1 = 17.0$ Hz, $J_2 = 7.4$ Hz, 3H, CH_3), 1.22 (s, 9H, *t*-Bu). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 177.6$ (d, $J = 5.0$ Hz, C=O), 53.0 (d, $J = 6.8$ Hz, OCH_3), 52.7 (d, $J = 6.8$ Hz, OCH_3), 40.1 (d, $J = 156.7$ Hz, CH), 38.5 (s, $\underline{C}(CH_3)_3$), 27.2 (s, $C(\underline{C}H_3)_3$), 15.4 (s, CH_3). ^{31}P NMR (242.8 MHz, $CDCl_3$): $\delta = 29.1$, identical by comparisons with literature data.[38]

Diethyl 1-(*N*-Pivaloylamino)ethanephosphonate (2b)

NMR experiment: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.93$ (d, $J = 8.7$ Hz, 1H, NH), 4.60–4.43 (m, 1H, CH), 4.20–4.05 (m, 4H, $O\underline{C}H_2CH_3$), 1.39–1.32 (m, 9H, $OCH_2\underline{C}H_3$, CH_3), 1.21 (s, 9H, *t*-Bu). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 177.4$ (d, $J = 5.4$ Hz, C=O), 62.3 (d, $J = 7.0$ Hz, $O\underline{C}H_2CH_3$), 62.2 (d, $J = 6.4$ Hz, $O\underline{C}H_2CH_3$), 40.4 (d, $J = 156.3$ Hz, CH), 38.5 ($\underline{C}(CH_3)_3$), 27.2 ($C(\underline{C}H_3)_3$), 16.3 (d, $J = 6.0$ Hz, $OCH_2\underline{C}H_3$), 16.2 (d, $J = 6.0$ Hz, $OCH_2\underline{C}H_3$), 15.5 (CH_3); identical by comparison with literature data.[39]

Dimethyl 1-(*N*-Benzyloxycarbonylamino)ethanephosphonate (2c)

Oil, 94.7 mg, 70%. IR (ATR), ν (cm^{-1}): 3243, 1717, 1538, 1231, 1043. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.37–7.29$ (m, 5H, Ph), 5.58 (d, $J = 9.6$ Hz, 1H, NH), 5.11 (s, 2H, OCH_2), 4.29–4.10 (m, 1H, CH), 3.74 (d, $J = 10.2$ Hz, 3H, OCH_3), 3.71 (d, $J = 10.5$ Hz, 3H, OCH_3), 1.38 (dd, $J_1 = 16.8$ Hz, $J_2 = 7.5$ Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.6$ (d, $J = 6.0$ Hz, C=O); 136.1, 128.3, 128.0, 127.9 – aromatic carbons; 66.9 (CH_2), 53.1 (d, $J = 7.6$ Hz, OCH_3), 52.8 (d, $J = 6.8$ Hz, OCH_3), 42.7 (d, $J = 158.6$ Hz, CH), 15.6 (CH_3). ^{31}P NMR (242.8 MHz, $CDCl_3$): $\delta = 28.5$, identical by comparison with literature data.[40]

Dimethyl 1-(*N*-Benzyloxycarbonylamino)-2-phenylethanephosphonate (2d)

NMR experiment: IR (ATR), ν (cm^{-1}): 3241, 2954, 1720, 1539, 1262, 1227, 1039. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$-7.17 (m, 10H, Ph), 5.12 (d, $J = 10.2$ Hz, 1H, NH), 5.00 (s, 2H, OCH_2), 4.43 (dddd, $J_1 = 16.0$ Hz, $J_2 = J_3 = 10.1$ Hz, $J_4 = 4.5$ Hz, 1H, CH), 3.74 (d, $J = 10.8$ Hz, 3H, OCH_3), 3.70 (d, $J = 10.5$ Hz, 3H, OCH_3), 3.23 (ddd, $J_1 = 13.8$ Hz, $J_2 = 9.1$ Hz, $J_3 = 4.7$ Hz, 1H, $C\underline{H}_2Ph$), 2.87 (ddd, $J_1 = 14.4$ Hz, $J_2 = J_3 = 10.1$ Hz, 1H, $C\underline{H}_2Ph$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.7$ (d, $J = 6.0$ Hz, C=O); 136.4, 136.2, 129.2, 128.4, 128.4, 128.0, 127.8, 126.8 – aromatic carbons; 66.9 (OCH_2), 53.2 (d, $J = 6.8$ Hz, OCH_3), 53.0 (d, $J = 6.8$ Hz, OCH_3), 48.2 (d, $J = 157.8$ Hz, CH), 35.8 (CH_2), identical by comparisons with literature data.[41]

Diethyl 1-(*N*-Benzyloxycarbonylamino)-2-phenylethanephosphonate (2e)

Oil, 140.1 mg, 76%. IR (ATR), ν (cm^{-1}): 3237, 1717, 1538, 1259, 1221, 1024. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.32–7.17$ (m, 10H, Ph), 5.58 (d, $J = 10.2$ Hz, 1H, NH), 4.98 (s, 2H, OCH_2), 4.39 (dddd, $J_1 = 15.9$ Hz, $J_2 = J_3 = 10.5$ Hz, $J_4 = 4.5$ Hz, 1H, CH), 4.15–3.97 (m, 4H, $OC\underline{H}_2CH_3$), 3.22 (ddd, $J_1 = 14.4$ Hz, $J_2 = 8.2$ Hz, $J_3 = 4.5$ Hz, 1H, $C\underline{H}_2Ph$), 2.89 (ddd, $J_1 = 14.4$ Hz, $J_2 = J_3 = 10.1$ Hz, 1H, $C\underline{H}_2Ph$), 1.27 (t, $J = 7.1$ Hz, 3H, $OCH_2C\underline{H}_3$), 1.21 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H}_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.7$ (d, $J = 6.0$ Hz, C=O); 136.7, 136.5, 136.3, 129.1, 128.2, 127.8, 127.7, 126.5 – aromatic carbons; 66.6 (OCH_2), 62.6 (d, $J = 6.8$ Hz, $O\underline{C}H_2CH_3$), 62.3 (d, $J = 6.8$ Hz, $O\underline{C}H_2CH_3$), 48.6 (d, $J = 157.0$ Hz, CH), 35.7 (CH_2), 16.2 (s, $OCH_2\underline{C}H_3$), 16.1 (s, $OCH_2\underline{C}H_3$). ^{31}P NMR (242.8 MHz, $CDCl_3$): $\delta = 24.5$, identical by comparison with literature data.[13]

Diethyl 1-(*N*-Benzyloxycarbonylamino)phenylmethanephosphonate (2f)

Colorless crystals, m.p.: 116-117 °C, 144.0 mg, 81%. IR (ATR), ν (cm^{-1}): 3235, 1713, 1547, 1250, 1231, 1025. ^1H NMR (300 MHz, $CDCl_3$): 7.47–7.26 (m, 10H, Ph), 6.26 (dd, $J_1 = 9.6$ Hz, $J_2 = 4.5$ Hz, 1H, NH), 5.17 (dd, $J_1 = 18.3$ Hz, $J_2 = 9.3$ Hz, 1H, CH), 5.14 (d, $J = 12.3$ Hz, 1H, OCH_2), 5.04 (d, $J = 12.3$ Hz, 1H, OCH_2), 4.16–3.99 (m, 2H, $OC\underline{H}_2CH_3$), 3.92–3.67 (m, 2H, $OC\underline{H}_2CH_3$), 1.24 (t, $J = 7.1$ Hz, 3H, $OCH_2C\underline{H}_3$), 1.07 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H}_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): 155.7 (d, $J = 8.3$ Hz, C=O); 136.1, 135.3, 128.5, 128.5, 128.0, 128.0, 127.9, 127.8 – aromatic carbons; 67.1 (OCH_2), 63.2 (d, $J = 7.6$ Hz, $O\underline{C}H_2CH_3$), 63.0 (d, $J = 7.6$ Hz, $O\underline{C}H_2CH_3$), 52.5 (d, $J =$

155.5 Hz, CH), 16.3 (d, $J = 6.0$ Hz, $OCH_2\underline{C}H_3$), 16.0 (d, $J = 5.3$ Hz, $OCH_2\underline{C}H_3$). ^{31}P NMR (242.8 MHz, $CDCl_3$): $\delta = 21.9$, identical by comparison with literature data.[42]

Ethyl [1-(*N*-pivaloylamino)ethyl]phenylphosphinate (3a)

Colorless crystals, m.p.: 120–121 °C, 95.2 mg, 68%. IR (ATR), ν (cm^{-1}): 2976, 1648, 1527, 1198, 1120, 1025. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.85$–7.42 (m, 5H, Ph[a]), 6.06 (d, $J = 9.3$ Hz, 1H, NH[b]), 5.80 (d, $J = 9.9$ Hz, 1H, NH[b]), 4.80–4.52 (m, 1H, CH[a]), 4.20–4.03 (m, 2H, $OC\underline{H}_2CH_3$[b]), 4.03–3.80 (m, 2H, $OC\underline{H}_2CH_3$[b]), 1.45 (dd, $J_1 = 14.6$ Hz, $J_2 = 7.4$ Hz, 3H, CH_3[b]), 1.21 (dd, $J_1 = 16.4$ Hz, $J_2 = 7.4$ Hz, 3H, CH_3[b]), 1.31 (t, $J = 7.1$ Hz, 3H, $OCH_2C\underline{H}_3$[b]), 1.30 (t, $J = 7.1$ Hz, 3H, $OCH_2C\underline{H}_3$[b]), 1.20 (s, 9H, *t*-Bu[b]), 0.91 (s, 9H, *t*-Bu[b]). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 177.7$ (d, $J = 5.3$ Hz, C=O[b]), 177.3 (d, $J = 5.3$ Hz, C=O[b]); 132.8 (d, $J = 2.3$ Hz), 132.6 (d, $J = 2.3$ Hz), 132.3 (d, $J = 9.8$ Hz), 132.0 (d, $J = 9.8$ Hz) 132.1, 132.0, 128.7 (d, $J = 12.8$ Hz), 128.7 (d, $J = 12.1$ Hz) – aromatic carbons[b]; 61.4 (d, $J = 7.0$ Hz, $OC\underline{H}_2CH_3$[b]), 61.3 (d, $J = 6.9$ Hz, $OC\underline{H}_2CH_3$[b]), 43.6 (d, $J = 75.5$ Hz, CH[b]), 43.6 (d, $J = 81.5$ Hz, CH[b]), 38.8 ($\underline{C}(CH_3)_3$[b]), 38.5 ($\underline{C}(CH_3)_3$[b]), 27.4 ($C(\underline{C}H_3)_3$[b]), 27.1 ($C(\underline{C}H_3)_3$[b]), 16.6 (d, $J = 6.0$ Hz, $OCH_2C\underline{H}_3$[b]), 16.4 (d, $J = 6.0$ Hz, $OCH_2C\underline{H}_3$[b]), 15.0 (CH_3[b]), 14.3 (CH_3[b]). ^{31}P NMR (242.8 MHz, $CDCl_3$): $\delta = 41.9$, 41.7. HRMS (EI) calcd. for $C_{15}H_{24}NO_3PNa$ $[M + Na]^+$: 320.1386, found 320.1400.

[a]Overlapping signals of two diastereomers. [b]One of two signals of two diastereomers.

Ethyl [1-(*N*-pivaloylamino)ethyl]ethylphosphinate (3b)

Resin, 79.8 mg, 68%. IR (ATR), ν (cm^{-1}): 3289, 2976, 1644, 1529, 1187, 1029. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.18$ (d, $J = 9.2$ Hz, NH[b]), 5.95 (d, $J = 8.8$ Hz, 1H, NH[b]), 4.50–4.38 (m, 1H, CH[a]), 4.17–4.02 (m, 2H, $OC\underline{H}_2CH_3$[a]), 1.77–1.66 (m, 2H, $PC\underline{H}_2CH_3$[a]), 1.38–1.34 (m, 3H, CH_3[a]), 1.34–1.30 (m, $OCH_2C\underline{H}_3$[a]), 1.22 (s, 9H, *t*-Bu[b]), 1.21 (s, 9H, *t*-Bu[b]), 1.19–1.09 (m, 3H, $PCH_2C\underline{H}_3$[a]). ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 177.9$ (d, $J = 4.0$ Hz, C=O[b]), 177.5 (d. $J = 5.0$ Hz, C=O[b]), 61.0 (d, $J = 7.0$ Hz, $OC\underline{H}_2CH_3$[b]), 60.9 (d, $J = 7.0$ Hz, $OC\underline{H}_2CH_3$[b]), 42.0 (d, $J = 98.5$ Hz, CH[b]), 41.9 (d, $J = 105.5$ Hz, CH[b]), 38.7 ($\underline{C}(CH_3)_3$[b]), 38.6 ($\underline{C}(CH_3)_3$[b]), 27.5 ($C(\underline{C}H_3)_3$[b]), 27.3 ($C(\underline{C}H_3)_3$[b]), 19.4 (d, $J = 89.4$ Hz, $P\underline{C}H_2CH_3$[b]), 19.2 (d, $J = 90.4$ Hz, $P\underline{C}H_2CH_3$[b]), 16.7 (d, $J = 5.0$ Hz, OCH_2CH_3[b]), 16.6 (d, $J = 5.0$ Hz, OCH_2CH_3[b]), 14.7 (d, $J = 1.5$ Hz, CH_3[b]), 13.9 (d, $J = 0.5$ Hz, CH_3[b]), 5.7 (d, $J = 5.0$ Hz, $PCH_2\underline{C}H_3$[b]), 5.6 (d, $J = 5.0$ Hz, $PCH_2\underline{C}H_3$[b]). ^{31}P NMR (242.8 MHz, $CDCl_3$): $\delta = 56.1$, 55.9. HRMS (EI) calcd. for $C_{11}H_{24}NO_3PNa$ $[M + Na]^+$: 272.1386, found 272.1400.

[a]Overlapping signals of two diastereomers. [b]One of two signals of two diastereomers.

Ethyl [1-(*N*-Benzyloxycarbonylamino)-2-*tert*-butoxyethyl]phenylphosphinate (3c)

Oil, 132.4 mg, 67%. IR (ATR), ν (cm^{-1}): 3225, 2975, 1716, 1537, 1194, 1024. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.83$–7.28 (m, 10H, Ph[a]), 5.40 (d, $J = 10.2$ Hz, 1H, NH[a]), 5.11 (d, $J = 12.0$ Hz, 1H, OCH_2[b]), 5.09 (d, $J = 12.0$ Hz, 1H, OCH_2[b]), 5.07 (d, $J = 12.6$ Hz, 1H, OCH_2[b]), 5.03 (d, $J = 12.0$ Hz, 1H, OCH_2[b]), 4.44–4.36 (m, 1H, CH[b]), 4.31–4.24 (m, 1H, CH[b]), 4.21–3.99 (m, 2H, $OC\underline{H}_2CH_3$[a]), 3.71–3.59 (m, 2H, CH_2[a]), 1.32 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H}_3$[b]), 1.29 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H}_3$[b]), 1.07 (s, 9H, *t*-Bu[b]), 1.05 (s, 9H, *t*-Bu[b]). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.8$ (C=O[b]), 155.6 (C=O[b]); 136.3[a], 132.4[b] (d, $J = 2.3$ Hz), 132.3[b] (d, $J = 2.3$ Hz), 132.0[a], 132.0[b] (d, $J = 10.6$ Hz), 131.9[b] (d, $J =$

9.8 Hz), 128.4[a], 128.4[b] (d, $J = 12.8$ Hz), 128.2[b] (d, $J = 11.3$ Hz), 128.0[a], 127.9[a] – aromatic carbons; 73.4 ($\underline{C}(CH_3)_3$[a]), 66.9 (CH_2[a]), 61.4 (d, $J = 6.8$ Hz, $OC\underline{H}_2CH_3$[b]), 60.1 (d, $J = 2.3$ Hz, $OC\underline{H}_2CH_3$[b]), 59.8 ($C_\beta H_2$[a]), 51.6 (d, $J = 80.8$ Hz, CH[b]), 50.2 (d, $J = 82.3$ Hz, CH[b]), 27.1 ($C(\underline{C}H_3)_3$[a]), 16.4 (d, $J = 5.3$ Hz, $OCH_2\underline{C}H_3$[b]), 16.3 (d, $J = 5.3$ Hz, $OCH_2\underline{C}H_3$[b]). ^{31}P NMR (242.8 MHz, $CDCl_3$): $\delta = 40.1$, 38.8. HRMS (EI) calcd. for $C_{22}H_{30}NO_5PNa$ $[M + Na]^+$: 442.1754, found 442.1764.

[a]Overlapping signals of two diastereomers. [b]One of two signals of two diastereomers.

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