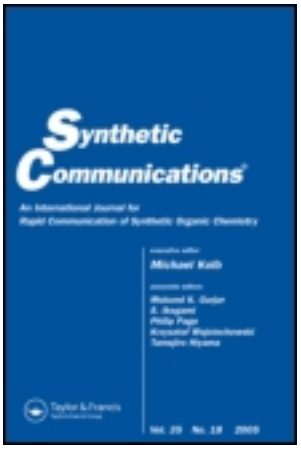

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New Catalyst for Phosphonylation of C=X Electrophiles

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NEW CATALYST FOR PHOSPHONYLATION OF C=X ELECTROPHILES

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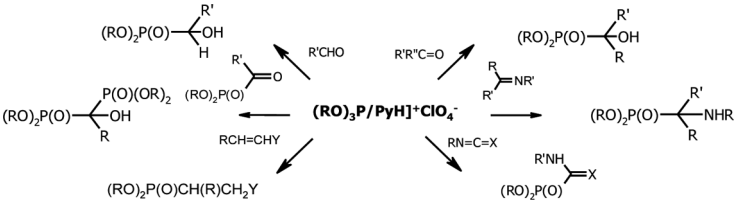
GRAPHICAL ABSTRACT



Abstract *Pyridinium perchlorate is found to be an efficient and recyclable catalyst for the reaction of trialkyl phosphites with various C=X electrophiles (aldehydes, ketones, ketophosphonates, imines, isocyanates, isothiocyanates, activated alkenes) to afford corresponding α-substituted phosphonates in good yields. The main advantages of the new catalyst is strong activity, accessibility, good yields of products, and gentle conditions of reaction.*

Keywords α-Aminophosphonates; bisphosphonates; catalysis; α-hydroxyphosphonates; pyridinium perchlorate

INTRODUCTION

Synthesis of functionalized phosphonates has attracted great attention because of their biological activity.[1–3] They act as peptide mimics, haptenes of catalytic antibodies, antibiotics and pharmaceuticals, herbicides, and enzyme inhibitors.[4] There are two main pathways for the synthesis of α-functionalized phosphonates: the reaction of dialkyl phosphites with nonsaturated electrophiles C=X in the presence of Brønsted bases or Lewis acids (Abramov reaction,[5,6] Kabachnik–Fields reaction,[7,8] and Pudovik reaction[9,10]) and the reaction of trialkyl phosphites with aldehydes or imines in the presence of Lewis acids.[7,11] However, in spite of their potential utility, these methods typically suffer from one or more disadvantages such as poor activity of dialkyl phosphites to ketones and ketimines. The reactions

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proceed with formation of various impurities formed under the effect of alkaline catalysts (phosphonate-phosphatic rearrangement,[11] retro-Abramov reaction,[12] and others). Besides, Lewis acids used as catalysts are moisture sensitive and require specialized handling and tedious workup.

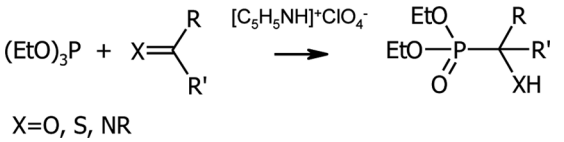
RESULTS AND DISCUSSION

In the present article, we propose the pyridinium perchlorate as a new, efficient, and universal catalyst for the phosphonylation of C=X electrophiles (X=O, S, NR, CR_2), by trialkyl phosphites (Scheme 1, Table 1). To our knowledge, this is the first case when ammonium or pyridinium salt catalyzes the reaction of trialkyl phosphites with electrophiles.[13]

In all cases, the reactions proceeded smoothly under solvent-free conditions or in a methylene chloride solution at room temperature to afford α-substituted phosphonates without undesired side products.[14] The pyridinium perchlorate increases the rate of reaction; however, it is not consumed by the reaction itself. It can be isolated from a reaction mixture and reused, and no significant decrease in its activity was noticed.

We have recently reported that pyridinium halogenides ($[C_5H_5NH]^+Hlg^-$, Hlg = I, Br, Cl) activate the reaction of trialkyl phosphites with C=X electrophiles.[15] However the pyridinium halogenides are reagents, because they are consumed in the course of reaction, whereas the pyridinium perchlorate is a catalyst. Scheme 2 explains the catalytic action of pyridinium perchlorate.

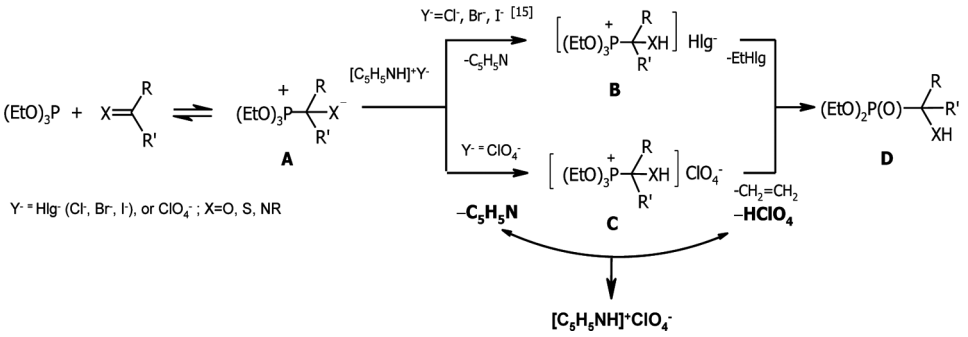
The nucleophilic attack of triethyl phosphite on the electron-deficient carbon of C=X group leads to the formation of betaine **A**, which reacts with pyridinium perchlorate to afford the alkoxyphosphonium perchlorate **C** and pyridine. Salt **C** is unstable and decomposes with the formation of phosphonate **D**, alkene, and perchloric acid, which reacts with pyridine to regenerate the pyridinium perchlorate. The quasiphosphonium intermediate **B** forming from pyridinium halogenides decomposes with formation of EtHlg. The pyridinium perchlorate more actively



Scheme 1. Phosphonylation of C=X electrophiles.

Table 1. Effect of anion nature in pyridinium salts on the reaction of triethylphosphite with cyclohexanone

$[C_5H_5NH]^+X^-$	X=Cl	X=Br	X=I	$X=ClO_4$
Reaction time (h)	12	12	6	5
Temperature (°C)	35	35	25	25
Yield (%)	55	70	85	92



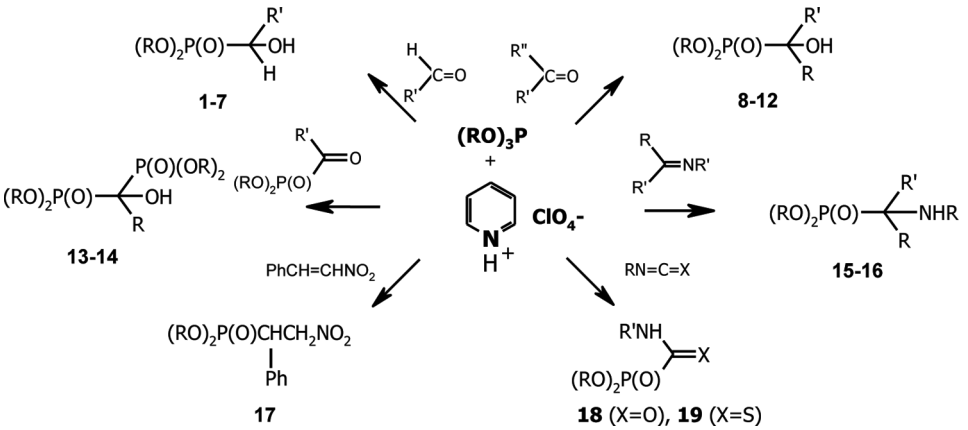
Scheme 2. Possible mechanism of catalysis by pyridinium perchlorate.

initiates the reaction of trialkylphosphites with C=X electrophiles than pyridinium halogenides. Utilization of pyridinium perchlorate instead of pyridinium halogenides considerably increases the reaction rate and increases yields (Table 1).

Pyridinium perchlorate can be easily prepared by reaction of pyridine with perchloric acid in a water solution. It is poorly soluble in water and can be easily filtered off as crystalline matter. After drying in a vacuum exsiccator, the pyridinium perchlorate is ready for utilization.

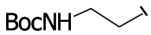
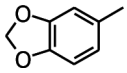
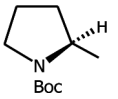
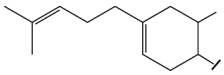
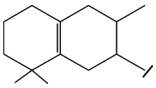
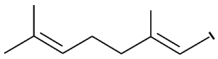
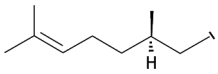
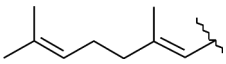
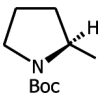
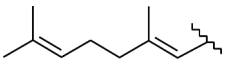
We give some typical examples of syntheses demonstrating the high effectiveness of pyridinium perchlorate as catalyst for the reaction of trialkylphosphites with C=X electrophiles (Scheme 3). Highly active catalysts allows to phosphonylate some low-active electrophiles, which are impossible to convert into phosphonates by known methods. The results are summarized in Table 2.

A number of aldehydes, including aromatic, aliphatic, and unsaturated aldehydes, underwent reactions with trialkyl phosphites in the presence of pyridinium perchlorate to afford the corresponding α-hydroxy-phosphonates **1**–**7** in good yields. The reaction is exothermic and should be performed at cooling to 0 °C or below. The formation of undesired side products was not observed. Only an insignificant



Scheme 3. Reaction of C=X electrophiles with $(RO)_3P$ catalyzed by pyridinium perchlorate.

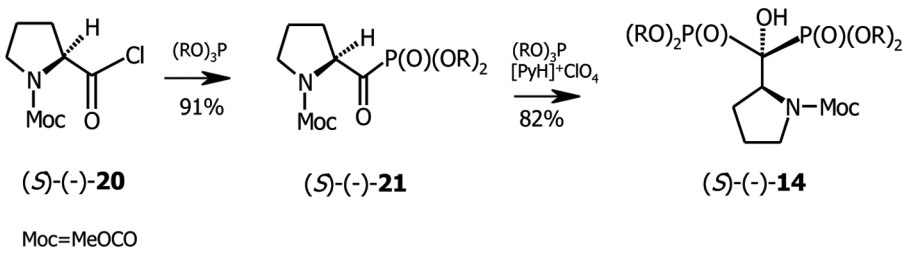
Table 2 Reaction conditions: $(R^1O)_3P + R^2R^3C{=}X + [C_5H_5NH]^+ClO_4^- \rightarrow (R^1O)_2P(O)C(XH)R^2R^3$

Compound	R^1	R^2	R^3	X	Temp. (°C)	Time (h)	Yield (%)[a]
1	Et		H	O	0–20	2	88
2	Me		H	O	0–20	2	89
3[b]	Me		H	O	0 – 20	2	85
4	Et		H	O	0–20	4	90
5	Et		H	O	0–20	4	90
6	Et		H	O	0–20	2	90
7	Et		H	O	0–20	2	90
8	Et	3-$F_3CC_6H_4$	Me	O	25	6	80
9	Et	4-t-BuC_6H_4	Me	O	25	12	70
10	Et	3,4-$(MeO)_2C_6H_3$	Et	O	50	12	80
11	Et			O	25	4	85
12	Et			O	25	4	85
13	Et		$(EtO)_2P(O)$	O	25	10	70
14	Et		$(EtO)_2P(O)$	O	25	6	75
15	Et		H	PhN	30	12	60
16	Me	Ph	H	BnN	28	12	71
17	Et	Ph	H	$CHNO_2$	0–20	6	65
18	Et	PrN=C		O	0–20	2	90
19	Et	$CH_2{=}CHCH_2N{=}C$		S	0–20	2	80

[a]Yields of purified products are shown.

[b]4:1 mixture of diastereoisomers as calculated from the ^1H and ^{31}P NMR (δ_P 23.03; 22.02 ppm) spectra of the crude product.

impurity of dialkyl phosphites is formed in some cases; however, it can be removed easily under vacuum to provide spectroscopically pure hydroxyphosphonates **1**–**7**. The pyridinium perchlotate initiates the reaction of triethyl phosphite with ketones,



Scheme 4. Synthesis of bisphosphonate (*S*)-**14**.

which normally produces poor yields of hydroxyphosphonates in the reaction with dialkyl phosphites because of their intrinsic lower reactivity. Because of the high catalytic activity of pyridinium perchlorate, the reaction of trialkyl phosphites with ketones proceeded under gentle conditions in good yields of corresponding hydroxyphosphonates **8**–**14**.

In the presence of pyridinium perchlorate, ketophosphonates react readily with trialkyl phosphites in methylene chloride at room temperature or at cooling to 0 °C with formation of 1-hydroxy-1,1-bis-phosphonates **13** and **14**.[15,16] The reaction is completed during several hours to afford in good yields the hydroxybisphosphonates **13** and **14**, bearing terpene or aminoacid residues. For example, the chiral bisphosphonate (*S*)-**14** was prepared starting from chloride N-Moc-L-proline **20** (Scheme 4).

The chloride N-Moc-L-proline **20** reacts easily with triethyl phosphite to furnish the chiral ketophosphonate (*S*)-**21**, which was purified by vacuum distillation and then converted in good yield into bisphosphonates (*S*)-**14** by reaction with triethyl phosphite in the presence of pyridinium perchlorate.

The reaction of $(EtO)_3P/[PyH]^+ClO_4^-$ with imines leads to the formation of aminophosphonates **15** and **16** under soft conditions (Table 2).[17] The reaction proceeds at 0 °C, more easily than the Kabachnik–Fields reaction of benzylbenzaldimine with diethyl phosphite, which ends only by heating to 140 °C for several hours.

The $(EtO)_3P/[PyH]^+ClO_4^-$ phosphonylates also ketimines, which are hard to reach by other methods (Table 2).[18]

Pyridinium perchlorate initiates the reaction of nitrostyrene with trialkyl phosphites in methylene chloride solution at 0 °C to afford the β-nitro-α-phenylethylphosphonates **17** in good yields.[19]

In the presence of $[PyH]^+ClO_4^-$, triethyl phosphite phosphonylate readily isocyanates and isothiocyanates at 0 °C in a solution of methylene chloride to convert them into carbamoylphosphonate **18**[6] or thiacarbamoylphosphonate **19** in good yields.

CONCLUSION

In summary, pyridinium perchlorate is a new and efficient catalyst for the reaction of trialkyl phosphites with C=X electrophiles. Utilization of pyridinium perchlorate allows phosphonylation of aldehydes, ketones, aldimines, ketimines, ketophosphonates, and certain alkenes with formation of functionalized phosphonates. Pyridinium perchlorate is stable, easy to handle, recoverable by simple

filtration, and recyclable. The advantages of this procedure are operational simplicity, wide substrate scope, and good yields of products. In many cases, pyridinium perchlorate allows us to obtain functionalized phosphonates, which are impossible to prepare by known methods. We believe that the method utilizing pyridinium perchlorate presents a practical alternative to existing procedures for the synthesis of α-functionalized phosphonates.

EXPERIMENTAL

^{1}H, ^{19}F, and ^{31}P NMR spectra were obtained on a Varian VXR-300 spectrometer at 300, 198, and 81 MHz, respectively. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker DRX-500 Avance Spectrometer at 500.1, 125.8, and 202.45 MHz, respectively. Thin-layer chromatography (TLC) was performed on aluminum-backed silica-gel TLC plates (250-mm layer) with ultraviolet visualization. All solvents were purified using standard methods; diethyl phosphite, dimethyl phosphite, aldehydes, ketones, amines, and aniline were purchased from Aldrich or Acros Organics and used without further purification.

Addition of Trialkyl Phosphites to C=X Compounds Under Solvent-Free Conditions (General Procedure)

Pyridinium perchlorate (~0.005 mol) was added to a mixture of C=X compounds (0.01 mol) and trialkyl phosphite (0.01 mol) at cooling to 0 °C, and the mixture was stirred for the indicated time as shown in Table 1. Then the reaction mixture was dissolved in methylene chloride or diethyl ether and filtered to give ~0.0049 mol of used catalyst. The solvent was removed under reduced pressure. The residue was used without special purification or distilled under vacuum, crystallized, or chromatographed on a column with silica gel.

Addition of Trialkyl Phosphites to C=X Compounds in Solvent (General Procedure)

Pyridinium perchlorate (~0.005 mol) was added to a solution of C=X compound (0.01 mol) and trialkyl phosphite (0.01 mol) at 0 °C, and the reaction mixture was stirred for the indicated time and temperature as shown in Table 1. Then the mixture was filtered, evaporated, and diluted with diethyl ether to give after filtration ~0.0049 mol of used catalyst. The solvent was evaporated under reduced pressure, and the residue was purified by distillation under vacuum, crystallized, or chromatographed on a column with silica gel.

Recyclability of Catalyst

The pyridinium perchlorate used in the experiment was washed with diethyl ether and dried under vacuum. Then the recovered pyridinium perchlorate (~0.005 mol) was added to the mixture of triethyl phosphite (0.01 mol) and benzaldehyde (0.01 mole) at cooling to 0 °C, and the reaction mixture was stirred ~2 h at room temperature. The catalyst was separated, and the residue was distilled under

vacuum to give the phosphonate **1** in 85% yield, bp 160 °C (0.05 mmHg), mp 83 °C. White solid.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.14$–1.27 (m, 6H), 3.94–4.08 (m, 4H), 5.00 (d, $J = 11.0$ Hz, 1H), 7.25–7.37 (m, 3H), 7.46–7.49 (m, 2H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.40$, 28.50, 33.01, 35.10, 62.00 (d, $J = 8$); 64.05 (d, $J = 160$). ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = 21.69$.

Analogously, the reaction of triethyl phosphite with cyclohexanone in the presence of recycled pyridinium perchlorate afforded the phosphonate **11**.

Yield 85%, bp 120 °C (0.08 mmHg), mp 61–63 °C.[15] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.30$ (t, 6H, $J = 7.2$, $\underline{CH_3}CH_2$), 1.52 (m, 2H, CH_2), 1.66 (m, 4H, CH_2), 1.87 (m, 4H, CH_2), 3.60 (br, 1H, OH), 4.16 (dq, 4H, $J = 7$, $J = 8$, OCH_2). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.45$ (d, $J = 6.25$), 20.20 (d, $J = 11.5$), 25.37; 31.51 (d, $J = 2.5$, CH_2), 62.51 (d, $J = 7.5$, OCH_2), 70.95 (d, $J = 147.5$, PC). ^{31}P NMR (80.95 MHz, $CDCl_3$): δ 26.9.

Diethyl 1-Hydroxy N-*tert*-Butoxycarbonyl-3-aminopropyl-Phosphonate (1)

Colorless oil, bp 160 °C (0.008 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.34$ (t, 6H, $J = 7$ Hz, CH_3), 1.44 [s, 9H, $(CH_3)_3C$], 1.89 (m, 2H, CH_2), 3.23 (m, 1H, NCH_2), 3.46 (m, 1H, NCH_2), 3.96 (m, 1H, PCH), 4.18 (m, OCH_2), 5.1 (br, 1H, OH). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.4$, 28.5, 33, 35, 62 (d, $J = 8$ Hz); 64 (d, $J = 160$ Hz). ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = 25.7$. Anal. calcd. for $C_{12}H_{26}NO_6P$: N, 4.50, P 9.95. Found: N 4.55, P 9.81.

Dimethyl (1,3-Benzodioxol-5-yl)-hydroxymethylphosphonic Acid (2)

Colorless solid, mp 91 °C ($CHCl_3$/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.7$ (d, $J = 15$ Hz, CH_3O), 5.36 (d, $J = 10$ Hz, HCH), 5.91 (s, 3H, CH_2O_2), 7.2–7.4 (m, C_6H_3). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 53$ (d, $J = 28$ Hz), 70 (d, 165 Hz), 101.1, 107.9 (d, $J = 21$ Hz), 120, 130, 147.48, 147.68. ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta_P = 28$. Calcd. for $C_{10}H_{13}O_6P$: C, 46.16; H, 5.04. Found: C, 46.34; H, 5.21.

Dimethyl (*S,R*)-2-N-Boc-pyrolidine(hydroxy)methyl-phosphonate (3)[16]

To 0.01 mol of trimethyl phosphite at −10 °C were added 0.01 mol of N-Boc-prolynale and 0.01 mol of pyridinium bromide. The reaction mixture was stirred 5 h at −10 °C, 2 h at 0 °C, and 1 h at rt. The reaction mixture was diluted with diethyl ether and filtered, and the residue was evaporated. Yield 95%, mixture of (*S,R*) and (*S,S*)-diastereomeres in ratio of 4:1. ^{31}P NMR ($CDCl_3$), δ, ppm 26.9 and 26.3. The product was purified by column chromatography on silica gel (EtOAc–hexane, 1:3), recrystallized in a −20 °C mixture of chloroform–hexane and then in hexane and resulted in pure (*S,R*)-diastereomer.

Mp 79 °C, $[\alpha]_D - 60$ (c 2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 1.8–2.3 (m, 4H), 3.2 (m, 1H), 3.7–3.8 (m, 2H), 3.7 (d, 6H, $J = 10$ Hz), 4.1 (m,

1H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 24.5$, 28.5, 28.8, 47.5, 53.0 (d, $J = 6.9$), 59.0, 73.5 (d, $J = 158.8$), 81.5, 159. ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta_P = 26.9$.

Diethyl Hydroxy[6-methyl-4-(4-methylpent-3-enyl)cyclohex-3-en-1-yl]methyl-Phosphonate (4)

Yield 80%. The product was purified by column chromatography on silica gel (EtOAc–hexane, 1:3) to afford the desired phosphonate. Colorless oil, bp 180 °C (0.08 mmHg). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.99$ (d, 3H, $J = 6$ Hz), 1.33 (t, 6H $J = 7$ Hz), 1.6 (s, 3H), 1.87 (s 3H), 1.91–2.22 (m, 10H), 3.51 (br, 1H), 4.17 (m, 5H, $J = 7$ Hz, $J = 8$ Hz), 6.28 (s, 1H), 5.32 (m, 2H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 8.87$, 16.28, 17.3, 25.4, 25.78, 27.01, 27.08, 29.96, 32.15, 33.69 (d, $J = 150$ Hz), 42.8, 61.81 (d, $J = 6$ Hz), 120.6, 123.9, 130.8, 135.59. ^{31}P NMR (80.95 MHz, $CDCl_3$: $\delta_P = 26.6$. Anal. calcd. for $C_{18}H_{33}O_4P$: C, 62.77; H, 9.66; P, 8.99. Found: C, 62.58; H, 9.55; P, 8.80.

Diethyl Hydroxy(3,8,8-trimethyl-1,2,3,4,5,6,7,8-octahydro-naphthalene-2-yl) Methylphosphonate (5)

Yield 80%, colorless solid, bp 190 °C (0.1 mmHg), mp 107–110 °C (hexane). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.957$ (d, 3H, J 6), 0.975 (s, 6H), 1.34 (t, 6H, $J = 7$ Hz), 1.43 (m, 2H), 1.6 (m, 4H), 1.8 (m, 2H), 1.9 (m, 1H), 2.0 (m, 1H), 2.19 (m, 2H), 2.91 (br, 1H), 4.2 (m, 5H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.4$, 19.27, 19.99, 24.87, 27.02, 27.07, 28.1, 28.97, 32.89, 33.73, 39.5, 48.9, 62.17 (d, $J = 6$ Hz), 62.17, 70.88 (d, $J = 160$ Hz), 127.2, 133.61. ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = 25.63$. Anal. calcd. for $C_{18}H_{33}O_4P$: C, 62.77; H, 9.66; P, 8.99. Found: C, 62.53; H, 9.54; P, 9.19.

Diethyl (2*E*)-1-Hydroxy-3,7-dimethyl-2,6-octadienyl-phosphonate (6)

Yield 80%, bp 135 °C (0.08 mm Hg). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J_{HH} = 7$ Hz), 1.29 (t, $J_{HH} = 7$ Hz), 1.61 (s, 3H), 1.69 (s, 3H); 2.1 (br, 4H), 4.12 (m, 4H), 4.52 (dd, 1H, $J_{HH} = 9$ Hz, $J_{HP} = 9$ Hz), 5.12 (br, 1H), 5.36 (br, 1H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.4$, 17.0, 17.6, 25.60, 26.7, 37.90, 37.9, 61.7, 61.8, 65.1, 66.1, 119.1, 124.0, 131.7, 138.8. ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = 24.19$. Anal. calcd. for $C_{14}H_{27}O_4P$: C, 57.92; H, 9.37. Found: C, 57.99; H, 9.49.

Diethyl (*S*$_P$,*R*/*R*$_P$,*R*)-(6*E*)-1-Hydroxy-3,7-dimethyl-2,6-octenyl-phosphonate (7)

Yield 80%, bp 145–150 °C (0.08 mmHg). Mixture of (*SpR*/*RpR*)-diastereomers. ^1H NMR (300 MHz, $CDCl_3$), $\delta = 0.96$ (d, 3H, $J = 7$ Hz), 1.29 (t, 3H, $J = 7$ Hz), 1.30 (t, 3H, $J = 7$ Hz), 1.58 (s, 3H), 1.65 (s, 3H), 1.83 (m, 2H), 1.96 (m, 2H), 3.82 (m, 1H), 4.09 (m, 4H), 5.07 (t, 1H, $J = 7$ Hz), 5.7 (br, 1H). ^{13}C NMR (125.74 MHz, $CDCl_3$): (*SpR*) $\delta = 16.45$, 16.49, 17.6, 20.25, 25.19, 25.52, 25.65, 28.30 d ($J = 12$ Hz), 35.75, 38.11, 62.51 d ($J = 7.5$ Hz), 62.64 d ($J = 6$ Hz), 65.59 d ($J = 158$ Hz), 124.70, 131.09;

(*RpR*) δ = 16.45, 16.49, 18.35, 20.25, 25.19, 25.52, 25.65, 29.0 (d, J = 12 Hz), 37.80, 38.56, 62.51 (d, J = 7.5 Hz), 62.64 (d, J 6 Hz), 66.06 (d, J = 157 Hz), 124.72, 131.13. ^{31}P NMR (202.45 MHz, $CDCl_3$): δ = 26.50, 26.54. Anal. calcd. for $C_{14}H_{29}O_4P$: P, 10.59. Found: P, 10.69.

Diethyl 1-Hydroxy-1-(3-trifluoromethylphenyl)ethylphosphonate (8)

Yield 80%. Purified by crystallization in hexane. Colorless crystalline, mp 125–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, 6H, J = 7 Hz), 1.83 (d, 3H, J = 15.6 Hz), 4.04 (m, 2H), 4.12 (m, 2H), 4.66 (br, 1H), 7.44–7.9 (m, 4H). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ = 16.17, 26.33, 63.5 (d, J = 94 Hz), 73.5 (d, J = 161 Hz), 127 (q, J = 271 Hz), 123.1, 123.88, 128.16, 130.01, 130.27, 143.00. ^{19}F NMR (196 MHz, $CDCl_3$): δ = −57.67. ^{31}P NMR (202.45 MHz, $CDCl_3$): δ_P = 25.3 (d, J = 8 Hz). Anal. calcd. for $C_{13}H_{18}F_3O_4P$: C, 47.86; H, 5.56; P, 9.49. Found: C, 47.55; H, 5.50; P, 9.65.

Diethyl 1-Hydroxy-1-(4-*tert*-butylphenyl)ethylphosphonate (9)

Yield 80%. Colorless crystalline, mp 84–86 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, 3H, J = 7 Hz) 1.17 (t, 3H, CH_3 J = 7 Hz), 1.24 (s, 9H), 1.8 (d, J = 14.5 Hz), 3.93 (m, 2H, OCH_2), 4.07 (m, 2H, OCH_2), 7.3–7.5 (m, 4H, C_6H_4). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ = 16.35, 25.83, 31.34, 34.44, 63.26 (d, J = 16 Hz); 73.4 (d, J = 158 Hz), 124.9, 125.55 (d, J = 4 Hz), 137.88, 150.24. ^{31}P NMR (80.95 MHz, $CDCl_3$): δ = 26.0. Anal. calcd. for $C_{16}H_{27}O_4P$: C, 61.13; H, 8.66; P, 9.85. Found: C, 61.01; H, 8.75; P, 9.65.

Diethyl [1-(3,4-Dimethoxyphenyl)-1-hydroxypropyl]phosphonate (10)

Purified by column chromatography on silica gel (EtOAc–hexane 1:3). Colorless oil, R_f 0.33. Yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (t, 3H, J = 7.2 Hz), 1.15 (t, 3H, J = 7 Hz), 1.27 (t, 3H, J = 7 Hz), 2.13 (dq, 1H, J = 7 Hz, J = 8 Hz), 2.24 (dq, 1H, J = 7 Hz, J = 8 Hz), 3.87 (s, 3H), 3.89 (s, 3H), 4.1 (m, 4H); 6.9–7.5 (m, 3H). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ = 9.09, 16.45, 27.82, 55.97, 62.35, 71.93, 72.94, 114.35, 116.59, 123.85, 125.3, 150.31, 151.02. ^{31}P NMR (80.95 MHz, $CDCl_3$): δ = 24.3. Anal. calcd. for $C_{15}H_{25}O_6P$: C, 54.21; H, 7.58%. Found: C, 54.16; H, 7.54%.

Diethyl 1-Hydroxycyclohexylphosphonate (11)

Yield 80%, bp 120 °C (0.1 mmHg), mp 71–73 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (t, 6H, J 7.2 Hz), 1.52 (m, 2H), 1.66 (m, 4H), 1.87 (m, 4H), 3.6 (br, 1H), 4.16 (dq, 4H, J 7 Hz, J 8 Hz). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ = 16.45 (d, J 6.25 Hz), 20.22 (d, J 11.5 Hz), 25.37; 31.5 (d, J 2.5 Hz), 62.5 (d, J 7.5 Hz), 70.95 (d, J 147.5 Hz). ^{31}P NMR (80.95 MHz, $CDCl_3$): δ_P = 26.93. Anal. calcd. for $C_{10}H_{21}O_4P$: C, 50.84; H, 8.96; P, 13.11. Found: C, 50.62; H, 8.91; P, 13.09.

Diethyl 4-Hydroxy(tetrahydro-2,2-dimethyl-2H-pyran-4-yl) phosphonate (12)

Yield 80%, bp 130–135 °C (0.08 mmHg), mp 72–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$ (s, 3H), 1.43 (s, 3H), 1.64–19 (m, 4H), 3.65 (m, 2H), 3.95 (br, 1H), 3.65 (m, 1H), 4.05 (m, 1H), 4.15 (dq, 4H, $J = 7$ Hz, $J = 8$ Hz). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.45$, 24.29, 31.909, 32.61, 39.87, 56.1 (d, $J = 12.5$); 62.8 (d, $J = 8.5$ Hz), 63.0 (d, $J = 7.5$ Hz), 70 (d, $J = 183.5$ Hz), 70.57. ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta_P = 23.6$. Anal. calcd. for $C_{11}H_{23}O_5P$: P, 11.63. Found: P, 11.63.

Tetraethyl (E)-1-Hydroxy-3,7-dimethylocta-2,6-diene-1,1-diyldiphosphonate (13)[20]

The product was purified by column chromatography on silica gel (EtOAc–hexane, 50:50) to afford the desired phosphonate. Yield 65%, oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (t, 6H, J 7 Hz), 1.28 (t, 6H, J 7 Hz), 1.6 (s, 3H), 1.63 (s, 3H), 1.8 (d, 3H, J_{HH} 8 Hz), 2.0 (m, 4H), 4.21 (m, 8H), 4.8 (m, 1H), 5.1 (t, 1H, J_{HH} 7 Hz). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.21$, 16.41, 17.59, 17.81, 25.61, 26.87, 36.9, 60.93, 64.53, 67.83, 71.13, 115.5, 124.03, 131.67, 139.77. ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = 23.3$. Anal. calcd. for $C_{18}H_{36}O_7P_2$: C, 50.70; H, 8.51; P, 14.53. Found: C, 50.45; H, 8.41; P, 14.40.

Bis(diethoxyphosphinyl)hydroxymethyl-N-(methoxycarbonyl)-1-pyrrolidine (14)

R_f 0.15 (EtAc/MeOH/C_6H_{12} = 1:1:1). $[\alpha]_D^{20} - 59$ (c 3.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.37$ (m, 12H), 1.68 (m, 1H), 1.91 (m, 1H), 2.37 and 2.65 (m, 2H, CH_2), 3.39 (m, 2H), 3.75 (s, 3H), 4.3 (m, 8H); 4.4 (m, 1H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.3$, 23.63, 29.50, 47.69, 53.18, 63.07, 63.23, 63.29, 63.50, 64.05 (t, J 62, CHN), 79.3 (t, J 153), 159.4. MS APCI, m/z (M + 1): 432.3 (calcd. M 431.3). ^{31}P-(^{1}H) NMR (202.45 MHz, $CDCl_3$), $\delta = 21.72$, 21.57, 20.94, 20.80 (rotamers and magnetic nonequivalence).

Dimethyl Phenyl[1-methyl[(benzyl)amino]methylphosphonate (15)[18]

Yield 70%, mp 60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.4$ (d, 3H, $J = 7$ Hz), 3.51 (m, 1H, NH), 3.79 (d, 3H, $J = 11.8$ Hz), 3.83 (d, 3H, $J = 10.1$ Hz), 5.2 (d, 1H, $J = 24$ Hz), 6.8–7.28 (m, 5H), 7.3 (d, 2H, $J = 8.5$ Hz), 7.5 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16$ (d, CH_3), 56.1 (d, $J = 7.0$ Hz), 56.2 (d, $J = 6.8$ Hz), 57.2 (d, $J = 150$ Hz), 114.3, 120.0, 128.2 (d, $J = 5.8$ Hz), 128.4 (d, $J = 3.1$ Hz), 130.1, 131.2, 140.0, 146.6 (d, J 14.5 Hz). ^{31}P NMR (80.95 MHz, $CDCl_3$): δ_P, 24. Anal. calcd. for $C_{17}H_{22}NO_3P$: C, 63.94; H, 6.94; N, 4.39. Found: C, 63.81; H, 6.92; N, 4.47.

Diethyl (2E)-1-Anilino-3,7-dimethylocta-2,6-dienylphosphonate (16)[19]

The product was purified by column chromatography on silica gel. Oil. Yield 50%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$–1.17 (m, 6H), 1.49 (s, 3H), 1.54 (s, 3H),

1.61 (s, 3H), 1.72–1.71 (m, 2H), 2.06–1.97 (m, 2H), 3.97–4.15 (m, 4H), 4.38 (dd, 1H, $J = 20.7$ Hz, $J = 9.4$ Hz), 4.95–5.12 (m, 2H), 6.54–7.13 (m, 5H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.4$, 16.5, 17.1, 17.7, 25.6, 26.2, 39.6, 50.6 (d, $J = 158.5$ Hz), 62.8 (d, $J = 7.3$), 63.1 (d, $J = 6.6$ Hz), 113.9, 118.4, 119.9, 123.6, 129.1, 131.8, 141.6, 146.8. ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = 28.4$. Anal. calcd. for $C_{20}H_{32}NO_3P$: N, 3.83; P, 8.48. Found: N, 3.72; P, 8.58.

Diethyl (2-Nitro-1-phenyl)ethylphosphonate (17)[20]

Yield 70%, mp 65 °C (hexane). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.2$, 37.46, 37.94, 61.74, 78.35, 127.3, 128, 128.9, 133.7. ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = 28.0$. Anal. calcd. for $C_{12}H_{18}NO_5P$: N, 4.96; P, 10.71. Found: N, 4.88; P, 10.78.

Diethyl (Propylamino)carbonylphosphonate (18)

Yield 90%, Colorless oil, bp 100–110 °C (0.08 mmHg). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, 3H, $J = 7.5$ Hz), 1.3 (t, 6H, $J = 7$ Hz), 1.51 (m, 2H), 3.2 (q, 4H, $J = 7$ Hz), 4.15 (m, 4H), 7.34 (br, 1H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 11.2$ (d, $J = 8$), 16.15 (d, $J = 15$ Hz), 22.6; 40.98, 64.15 (d, $J = 8$ Hz); 165 (d, $J = 221$ Hz). ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = -0.71$. Anal. calcd. for $C_8H_{18}NO_4P$: N, 6.28; P, 13.88. Found: N, 6.40; P, 13.68.

Diethyl (Allylamino)thiocarbonylphosphonate (19)

Yellowish liquid. Yield 80%, bp 120 °C (0.08 mmHg). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (t, 6H, J 7), 4.08–4.3 (m, 6H); 5.27 (dd, 1H, $J = 6$ Hz, $J = 1$ Hz); 5.31 (dd, 1H, $J = 12.5$ Hz, $J = 1$ Hz), 5.91, ddt, 1H, $J = 17$ Hz, $J = 10.2$ Hz, $J = 6$ Hz), 9.27 (br, 1H). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 16.24$ (d, J 10 Hz), 42.4 (d, J 9 Hz), 63 (d, $J = 6$ Hz); 119, 130.7, 193 (d, $J = 155$). ^{31}P NMR (80.95 MHz, $CDCl_3$): $\delta = -1.7$. Anal. calcd. for $C_8H_{16}NO_3PS$: N, 5.90; P, 13.05. Found: N, 5.88; P, 13.37.

Diethyl N-(Methoxycarbonyl)-1-pyrrolidineketophosphonate (21)

To 0.02 mol of N-Moc-L-proline chloride **20** was added 0.04 mol of triethyl phosphite at −20 °C. Then the temperature was raised to room temperature, and the reaction mixture was left for 2 h. After that the mixture was distilled under vacuum. Yield 85%, bp 140 °C (0.08 mmHg). Colorless liquid. $[\alpha_D{}^{20} - 44$ (c 2, $CHCl_3)$. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.37$ (m, 6H), 1.9 (m, 2H), 2.2 (m, 2H); 2.2 (m, 2H), 3.59 s, 3.71 s (3H, CH_2), 4.24 m (3H, OCH_2), 4.81 m, 4.87 m (1H, CHN). ^{13}C NMR (125.74 MHz, $CDCl_3$): $\delta = 17.8$, 28.89, 29.31, 29.53, 30.63, 46.39, 46.90, 52.21, 52.27, 63.30, 63.35, 63.55, 63.61, 154.25, 155.04, 208.8 (d, J 157.5 Hz), 208.6 (d, J 160 Hz). ^{31}P NMR (202.45 MHz, $CDCl_3$): $\delta_P = -2.98$ and −2.78 (rotamers). Anal. calcd. for $C_{11}H_{20}NO_6P$: N, 4.78; P, 10.56. Found: N, 4.61; P, 10.67.

REFERENCES

1. Engel, R. Phosphorus addition at sp^2 carbon. *Org. React. N.Y.* **1988**, *36*, 176–251; (b) Engel, R.; Cohen, J. I. *Synthesis of Carbon–Phosphorus Bonds*, 2nd ed.; CRC Press: Boca Raton, FL, 2004.
2. Kolodiazhnyi, O. I. Asymmetric synthesis of hydroxyphosphonates. *Tetrahedron: Asymmetry* **2005**, *16*, 3295–3340; (b) Kolodiazhnyi, O. I. Chiral hydroxyphosphonates: Synthesis, configuration, and biological properties. *Russ. Chem. Rev.* **2006**, *75*, 227–253.
3. Wiemer, D. F. Synthesis of nonracemic phosphonates. *Tetrahedron* **1997**, *53*, 16609–16644; (b) Cermak, D. M.; Du, Y.; Wiemer, D. F. Synthesis of nonracemic dimethyl α-(hydroxyfarnesyl)phosphonates via oxidation of dimethyl farnesylphosphonate with (camphorsulfonyl)oxaziridines. *J. Org. Chem.* **1999**, *64*, 388–393.
4. Bilenko, V.; Spannenberg, A.; Baumann, W.; Komarov, I.; Boerner, A. New chiral monodentate phosphsolane ligands by highly stereoselective hydrophosphination. *Tetrahedron: Asymmetry* **2006**, *17*, 2082–2087; (b) Shibasaki, M.; Kanai, M. Multifunctional asymmetric catalysis. *Chem. Pharm. Bull.* **2001**, *49*, 511–524.
5. Abramov reaction from Wikipedia: http://en.wikipedia.org/wiki/Abramov_reaction.
6. (a) Savignac, P.; Iorga, B. *Modern Phosphonate Chemistry*; CRS Press: Boca Raton, FL, 2003; (b) Gou, S.; Zhou, X.; Wang, J.; Liu, X.; Feng, X. Asymmetric hydrophosphonylation of aldehydes catalyzed by bifunctional chiral Al(III) complexes. *Tetrahedron* **2008**, *64*, 2864–2870; (c) Keglevich, G.; Tóth, V. R.; Drahos, L. Microwave-assisted synthesis of α-hydroxy-benzylphosphonates and α-benzylphosphine oxides. *Heteroatom Chem.* **2011**, *22*, 15–17.
7. Galkina, I. V.; Zvereva, E. R.; Galkin, V. I.; Cherkasov, R. A. Kinetics and mechanism of the Kabachnik–Fields reaction, III: Effect of the nature of the carbonyl compound on the kinetics and mechanism of the Kabachnik–Fields reaction: A unified reaction mechanism. *J. Russ. Gen. Chem.* **1998**, *68*, 1391; (b) Cherkasov, R. A.; Galkin, V. I. The Kabachnik–Fields reaction: Synthetic potential and the problem of the mechanism. *Russ. Chem. Rev.* **1998**, *67*, 857; (c) Keglevich, G.; Szekrényi, A. Eco-friendly accomplishment of the extended Kabachnik–Fields reaction: A solvent- and catalyst-free microwave-assisted synthesis of α-aminophosphonates and α-aminophosphine oxides. *Lett. Org. Chem.* **2008**, *5*, 616–622.
8. (a) Ma, J. Catalytic asymmetric synthesis of α- and β-amino phosphonic acid derivatives. *Chem. Soc. Rev.* **2006**, *35*, 630–636; (b) Ordonez, M.; Rojas-Cabrera, H.; Cativiela, C. An overview of stereoselective synthesis of α-aminophosphonic acids and derivatives. *Tetrahedron* **2009**, *65*, 17–49.
9. Pudovik, A. N.; Konovalova, I. V. Addition reactions of esters of phosphorus(lIl) acids with unsaturated systems. *Synthesis* **1979**, 81–96.
10. Quin, L. D. *A Guide to Organophosphorus Chemistry*; John Wiley and Sons: New York, 2000; p. 146.
11. Hammerschmidt, F.; Schmidt, S. The phosphonate–phosphate and phosphate–phosphonate rearrangement and their applications, V: On the reaction of s-butyllithium/TMEDA with symmetrical trialkyl phosphates. *Monatsh. Chem.* **1997**, *128*, 1173–1180.
12. Gancarz, R.; Gancarz, I.; Walkowiak, U. On the reversibility of hydroxyphosphonate formation in the Kabachnik–Fields reaction. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1995**, *104*, 45–52.
13. Kolodiazhna, O. O.; Kolodiazhna, A. O.; Kolodiazhnyi, O. I. Highly effective catalyst for the reaction of trialkyl phosphites with C=X electrophiles. In *Book of Abstracts*: 18th International Conference on Phosphorus Chemistry (ICPC-2010), P. Kafarski (Ed.); Wroclaw, 2010, p. 156.

14. Kolodiazhnyi, O. I. New methods for the synthesis of phosphonic analogues of natural compounds. *Phosphorous Sulfur Silicon Relat. Elem.*, **2011**, *186*, 644–651.
15. Kolodiazhna, O. O.; Kolodiazhna, A. O.; Kolodiazhnyi, O. I. An efficient method for the phosphonation of C=X compounds. *J. Russ. Gen. Chem.* **2010**, *80*, 709–722.
16. Van der Veken, P.; Senten, K.; Kertèsz, I.; Haemers, A.; Augustyns, K. Fluorinated proline derivatives: Potential transition state inhibitors for proline selective serine dipeptidases. *Tetrahedron Lett.* **2003**, *44*, 969–972
17. Gilmore, W. F.; McBride, H. A. Synthesis of an optically active α-aminophosphonic acid. *J. Am. Chem. Soc.* **1972**, *94*, 4361.
18. Xia, M.; Lu, Y.-D. Ultrasound-assisted one-pot approach to α-amino phosphonates under solvent-free and catalyst-free conditions. *Ultrason. Sonochem.* **2007**, *14*, 235–240.
19. Mastrukova, T. A.; Lazareva, M. V.; Perekalin, V. V. Synthesis of nitro- and aminoalkylphosphonates. *Russ. Chem. Bul.* **1972**, 1114–1116.
20. Kolodiazhna, O. O.; Kolodiazhnyi, O. I. Synthesis of isoprenyl bis(phosphonates). *J. Russ. Gen. Chem.* **2009**, *79*, 862–863.