Full factorial optimization of α-aminophosphonates synthesis using diphenylphosphinic acid as efficient Organocatalyst

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Abstract

Diphenylphosphinic acid is used as an efficient and simple catalyst for the synthesis of the *α*-aminophosphonates by multicomponent *Kabachnik-Fields* reaction in one pot of aromatic aldehyde, aniline and diethylphosphite. Three physicochemical factors including catalyst amount, reaction time and medium temperature were optimized using a full factorial experiment design (FFD). Additionally, a quadratic polynomial regression model was applied for the analysis of the experimental data at a confidence level of 95% with *p*-values < 0.05. The high signification effect of the reaction time and the medium temperature on the *α*-aminophosphonates synthesis were confirmed by the statistical analysis. Besides, the diphenylphosphinic acid amount shows an effect on the reaction yield. ANOVA exhibit that the coefficient determination of this model up to 99.25%. This eco-friendly procedure was extended for the preparation of series of the *α*-aminophosphonates in ethanol as green solvent, giving the desired products with high chemical yields up to 90%.

1. Introduction

As an important class in organic synthesis, medicinal chemistry and biological activities, organophosphorus compounds attract an intensively growing interest and fascinating applications in agricultural and industrial [1–3]. The *α*-aminophosphonates represent, from its discovery by *Kabachnik-Fields* in 1952 [4–5] to nowadays an important class of organophosphorus compounds due to their analogs amino acid, and mimic transition states of active peptides [6–8]. The *α*-aminophosphonates show an outstandingly broad spectrum of pharmacological and physiological effectiveness [9–11], and they are used as inhibitors of the angiotensin-converting enzyme [12], antiviral [13], antibiotic [14], antibacterial [15], antitumoral [16], anti-HIV [17], antihypertensive [18], anti-tuberculosis agents [19], anti-oxidant [20–21], anticorrosion [22], herbicides, fungicides and insecticides [23–24]. In reactivity terms, the *α*-aminophosphonates are used as a key intermediate in HWE reaction [25], as organocatalyst in the Petasis Boronic Acid *Mannich reaction* [26], in asymmetric *Michael* addition [27], and for the preparation of complexes as tridentate ligands [28].

Meanwhile, the multicomponent reaction via *Kabachnik-Fields* is still a crucial and highly valuable method for their synthesis using a wide range of catalysts, such as *Lewis* and *Brønsted* acids [29–31], organocatalysts [32–34], nano-materials [35], heteropolyacids [36] and *β*-cyclodextrin [37].

Due to the overwhelming development of the *α*-aminophosphonates in synthetic and biological fields, the efficient catalysts are widely requested for their preparation and increase their productivity. Unfortunately, few investigations are dedicated to developing this multicomponent reaction under green conditions; many reactions used costly catalysts, a stoichiometric amount of catalysts, long reaction time, and production of by-products. The last one can cause a considerable ecological problem related to their chemical proprieties. Therefore, the development of a new effective catalytic process using a low-cost and eco-friendly catalyst is considered a valuable approach to preparing these compounds.

In the continuation of our ongoing research interest for novel synthetic derivatives of organophosphorus compounds [38–42], we report the successful employ of diphenylphosphinic acid as an efficient catalyst in multicomponent condensation reaction aromatic aldehyde, aniline, and diethylphosphite. However, the diphenylphosphinic acid was previously tested in multicomponent reaction and the desired product is obtained with 76% chemical yield [43]. Nevertheless, this catalytic process is sensitive to various operational parameters, including the catalyst amount, reaction time and medium temperature. Studying the effect of each factor alone is considered a rather tedious, waste of effort, time and money. For these reasons, we have opting to use the full factorial design for diminution of the experimental difficulties by the optimization of all the affecting parameters together at the same time to optimize the effectiveness of our proposed target under green conditions reaction.

2. Experimental Section

2.1. General

All reagents were purchased from Sigma-Aldrich or Acros Company used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) using ultraviolet light (254 nm) as the visualizing agent and $KMnO_4$ solution as developing agents. NMR spectra were recorded with Bruker spectrometers operating at (400 MHz, 360 MHz, 300 MHz, and 250 MHz for 1H, 90 MHz, 75 MHz or 63 MHz for ^{13}C, and 162 MHz, 101 MHz or 121 MHz for ^{31}P). The chemical shift of Solvent reference peaks used were $CDCl_3$ (δ = 7.26 ppm) for 1H and (δ = 77ppm) for ^{13}C NMR spectra, while H_3PO_4 was used as external standard for chemical shift references for ^{31}P NMR. Couplings constants (*J*) are given in Hz, with the Following abbreviations multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. Mass spectra were taken by a MicrOTOF-Q Bruker spectrometer using electrospray ionization (ESI) analysis. Melting points were measured using Buchi Melting Point B-545.

2.2. General procedure for the synthesis of α-aminophosphonates 4a-4i.

The diphenylphosphinic acid (10 mol%) was added to the reaction mixture of aromatic aldehyde (122.12 mg, 1 mmol), aniline (93 mg, 1 mmol) and diethylphosphite (165 mg, 1.2 mmol) in ethanol (10 mL). The reaction was stirred at 40°C for 30 min. The progress of the reaction was monitored by TLC. The solvent was removed and the resulting residue was treated with HCl (1N) then washed with water (10 mL) and extracted with dichloromethane (10 mL×2). The organic phases were combined and evaporated in vacuum. The crude product was purified by crystallization in hexane. Complete experimental data have been provided (NMR spectra and HRMS).

2.2.1. Diethyl [Phenyl(phenylamino)methyl] phosphonate (4a)

Yield: 92%, as a white crystalline solid; mp 88°C. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C) δ 7.52–7.29 (m, 6H, ArH), 7.16–7.10 (t, 1H, J = 7.9 Hz, ArH), 6.75–6.69 (t, 1H,, J = 7.3 Hz, ArH), 6.64–6.61 (m, 2H, ArH), 4.84–4.75 (d, 1H, J_{HP}= 24.3 Hz, CHP), 4.18–4.10 (2H, m, -OCH_2- CH_3), 4.01–3.76 (2H, m, -OCH_2- CH_3), 3.74–3.63 (1H, m, -OCH_2 CH_3), 1.31 (t, 3H, *J* = 7.1 Hz, -OCH_2-CH_3), 1.14 (t, 3H, *J* = 7.1 Hz, -OCH_2-CH_3). ^{13}C NMR (63 MHz, $CDCl_3$, 25°C) δ 146.33 (d, J = 14.5 Hz); 136.00, 129.29, 128.74, 128.71, 128.00, 127.03, 118.40, 113.87, 63.27 (d, J^2_{CP} = 6.9 Hz), 57.29, 54.90, 16.46, (d, J^3_{CP} = 15.1), 16.37 (d, J^3_{CP} = 5.6 Hz). ^{31}P NMR (101 MHz, $CDCl_3$, 25°C) δ 22.46 ppm. HRMS (ESI) m/z calcd for $C_{17}H_{23}NO_3P$ [M + H^+]: 320.1408; Found 320.1410.

2.2.2. Diethyl (3-methoxyphenyl) (phenylaminomethyl) phosphonate (4b)

Yield: 98%, as a white crystalline solid; mp103°C.^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.36–7.30 (m, 2H, HAr), 7.07–7.13 (m, 2H, HAr), 6.85 (d, *J* = 7.3 Hz, 2H, H Ar), 6.66 (t,

J = 16.0 Hz, 1H, HAr), 6.58 (d, 2H, *J* = 8.5Hz, HAr), 4.72 (d, *J* = 24.4 Hz, 1H, CHP), 4.15 (m, 2H, OCH_2-CH_3), 3.91 (m, 1H, -OCH_2-CH_3), 3.77 (s, 3H, -OCH_3), 3.65–3.74 (m,

1H, -OCH_2-CH_3), 1.28 (t, 3H, *J* = 7.0 Hz, -OCH_2-CH_3), 1.14 (t, 3H, *J* = 7.0 Hz, -OCH_2-CH_3). ^{13}C NMR (75 MHz,$CDCl_3$, 25°C) δ 159.40, 143.54 (d, *J* = 15.4 Hz), 129.24, 129.08, 129.01, 127.77, 127.73, 118.43, 114.16, 114.13,63.39 (dd, J^2_{CP} = 6.9, 3.9 Hz), 56.45, 55.33, 54.43, 16.60 (d, $J^3_{C\,P}$ = 14.9Hz), 16.52 (d,J^3_{CP} = 5.9 Hz).^{31}P NMR (121 MHz, $CDCl_3$, 25°C) δ 23.47 ppm.

2.2.3. Diethyl [4-nitrophenyl(phenylamino)methyl]phosphonate (4c)

Yield: 90%, as a yellow crystalline solid; mp 89.2°C. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.22–8.19 (d, 2H, ArH), 7.68–7.64 (dd, 2H, J_{HP} = 8.9, 2.3 Hz, ArH), 7.19–6.95 (m, 2H, ArH), 6.76–6.71 (t, 1H, *J* = 7.4 Hz, ArH), 6.56–6.52 (m, 2H, ArH), 4.88–4.81 (d, 1H, J_{HP} = 25.6 Hz, CHP), 4.25–4.11 (m, 2H, OCH_2-CH_3), 3.99–4.02 (m, 1H, -OCH_2-CH_3), 3. 97 − 3. 78 (m, 1H, -OCH_2-CH_3), 1.32 (t, 3H, J = 7.1 Hz, -OCH_2-CH_3), 1.21 (t, 3H, J = 7.1Hz, -OCH_2-CH_3). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.59, 145.71 (d, J = 16.6 Hz), 143.92 (d, *J* = 2.5 Hz), 129.35, 128.64 (d, *J* = 4.7 Hz), 123.75, 119.12, 113.81, 63.63 (dd, J^2 = 27.4, 6.8 Hz), 56.78, 55.31, 16.34 (dd, J^3cp = 17.2, 5.5 Hz). ^{31}P NMR (162 MHz, Chloroform-*d*) δ 20.80. HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_5P$ [M + H+]: 387.1094; Found 387.1080.

2.2.4. Diethyl[1-naphtyl(p-tolylamino)methyl]phosphonate (4d)

Yield: 90%, as a white crystalline solid; mp 145°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.27 (d, 1H, J_{HP} = 8.5 Hz, ArH), 7.91 (d, 1H, *J* = 7.9 Hz ArH), 7.80–7.77 (m, 2H, ArH), 7. 63 − 7. 48 (m, 2H, ArH), 7.45 (t, 1H, *J* =

7.7 Hz, ArH), 6.67 (d, 2H, *J* = 8.48 Hz, ArH), 6.48 (d, 2H, *J* = 8.4 Hz, ArH), 4.64 (d, 1H, J_{HP} = 24.0 Hz, H_{CP}), 4.23–4.15 (m, 2H, $-OCH_2-CH_3$), 3.77–3.73 (m, 1H, $-OCH_2-CH_3$), 3. 28-3.17 (m, 1H, $-OCH_2-$ CH_3), 2.16 (s, 3H, CH_3-Ph), 1.34 (t, 3H, *J* = 7.1 Hz, $-OCH_2-CH_3$), 0.75 (t, 3H, *J* = 7.1 Hz, $-OCH_2-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.83 (d, *J* = 24.8 Hz), 133.81, 131.6 (d, *J* = 19.7 Hz), 129.70, 129.00, 128.40, 127.50, 126.22, 125.64, 125.35 (d, *J* = 6.0 Hz), 123.00, 113.67, 63.63 (dd, J^2_{CP} = 27.4, 6.8 Hz), 20.33, 16.49 (dd, J^3cp = 5.9, 5.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 23.07 ppm. HRMS (ESI) *m/z* calcd for $C_{22}H_{26}NO_3P$ [$M^+ H^+$]: 406.1532; Found 406.1542.

2.2.5. Diethyl [benzo [1, 3]dioxol-5-yl((p-tolylamino) methyl]phosphonate (4e)

Yield: 91%, as a white crystalline solid; mp 115°C. ^{1}H NMR (300 MHz, Chloroform-*d*): δ 7.51–7.33 (m, 1H, ArH), 7.00–6.89 (m, 4H, ArH), 6.78 (d, *J* = 8.0 Hz, 1H, ArH), 6.53 (d, *J* = 8.5 Hz, 2H, ArH), 5.97–5.91 (m, 2H,O-CH_2-O), 4.66 (d, J_{HP} = 24.0 Hz, 1H, H_{CP}), 4.22–4.07 (m, 4H,-OCH_2-CH_3), 4.06–3.93 (m, 1H, -OCH_2-CH_3), 3.87–3.72 (m, 1H, -OCH_2-CH_3), 2.21 (s, 3H, CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, $-OCH_2-CH_3$), 1.19 (t, *J* = 7.1 Hz, 3H, $-OCH_2$-CH_3). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 147.64 (d, *J* = 49.1 Hz), 143.78, 129.74 (d, *J* = 11.6 Hz), 121.35 (d, *J* = 6.5 Hz), 113.99, 108.21 (d, *J* = 13.9 Hz), 101.10, 63.84–62.26 (m), 57.01, 54.99, 20.36, 16.37 (dd, J^3cp = 12.4, 5.7 Hz). HRMS (ESI) *m/z* calcd for $C_{19}H_{24}NNaO_5P$ [M^+ Na^+]: 400.128430; Found 400.1273. ^{31}P NMR (121 MHz, Chloroform-*d*) δ 22.72.

2.2.6. Diethyl [(4-fluorophenyl)(4-tolylamino)methyl] phosphonate (4f)

Yield: 88%, as a white crystalline solid; mp 119°C. ^{1}H NMR (300 MHz, Chloroform-*d*): δ 7.43 (dd, J = 12.0, 4.0 Hz, 2H, H Ar), 7.26 (m, 2H, HAr), 6.93 (d, 2H, *J* = 8.2 Hz, HAr), 6.48 (d, 2H, *J* = 8.5 Hz, HAr), 4.64–4.78 (m, 2H, CH + NH), 4.10–4.17 (m, 2H, -OCH_2-CH_3), 3.97–4.05 (m, 1H, -OCH_2-CH_3), 3.79–3.85 (m, 1H, -OCH_2-CH_3), 2.21 (s, 3H,

CH_3–Ph), 1.31 (t, 3H, *J* = 7.1 Hz, -OCH_2-CH_3), 1.18 (t, 3H,

J = 7.1 Hz, -OCH_2-CH_3). ^{13}C NMR: (75 MHz, $CDCl_3$, 25°C): δ 143.85 (d, *J* = 15.0 Hz), 134.84, 133.80, 133.76, 133.71, 129.83, 129.28,128.21,127.89,127.86, 128.03, 114.06, 63.59 (dd, J^2_{cp} = 12.1,7.0 Hz),56.89,54.89,20.47,16.59(d, J^3_{cp} = 13.7 Hz), 16.52 (d, J^3_{cp} = 5.8 Hz). ^{31}P NMR (121 MHz, Chloroform-*d*) δ 22.69. HRMS (ESI) *m/z* calcd for $C_{18}H_{23}FNNaO_3P$ [M^+ Na^+]: 374.1291; Found 374.1275. ^{31}P NMR (121 MHz, Chloroform-*d*) δ 22.72.

2.2.7. Diethyl [(phenyl)(4-trifluoromethylamino)methyl] phosphonate (4g)

Yield: 88%, as white crystalline solid. mp 140°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): d = 1.12 (t, 3H, *J* = 7.0 Hz, $-OCH_2-CH_3$), 1.31 (t, 3H, *J* = 7.1 Hz, $-OCH_2-CH_3$), 3.61–3.70

(m, 1H, $-OCH_2-CH_3$), 3.90–4.08 (dd, *J* = 10.1,7.1Hz, 1H, -OCH_2-CH_3), 4.10–4.20 (m, 2H, $-OCH_2-CH_3$), 4.79 (dd, 1H, *J* = 24.2, 7.5 Hz, Ph–CH), 5.16–5.31 (m, 1H, NH), 6.62 (d, 2H, *J* = 8.5 Hz, HAr), 7.26–7.40 (m,5H,HAr),7.49 (dd, *J* = 7.7, 2.1 Hz, 2H, HAr). ^{13}CNMR (75MHz, $CDCl_3$, 25°C): δ 148.90 (d, *J* = 14.4 Hz), 135.13 (d, *J* = 3.0 Hz), 128.91, 128.87, 128.38, 128.34, 127.90, 127.83, 126.68, 126.63, 113.16, 63.75 (dd, J^2_{cp} = 22.9, 7.0 Hz), 56.77, 54.77, 16.59 (d, J^3_{cp} = 19.0 Hz), 16.51 (d, J^3_{cp} = 5.8 Hz). ^{31}P NMR: (121 MHz, $CDCl_3$, 25°C): δ 22.54 ppm.

2.2.8. Diethyl [3-phenoxyl(phenylamino)trifluoromethyl] phosphonate (4h)

Yield: 78%, as white crystalline solid. mp 155°C. ^{1}H NMR (360 MHz, Chloroform-*d*) δ 7.43–7.25 (m, 5H, ArH), 7.20 (d, *J* = 7.5 Hz, 1H, ArH), 7.13–7.05 (m, 3H, ArH), 6.93 (d, *J* = 7.6 Hz, 2H, ArH), 6.59 (d, *J* = 8.6 Hz, 2H, ArH), 4.74 (d, *J* = 24.4 Hz, 1H, HC*), 4.20–4.06 (m, 2H), 4.05–3.93 (m, 1H, $-OCH_2-CH_3$), 3.84– 3.69 (m, 1H, $-OCH_2-CH_3$), 1.29 (t, *J* = 7.1 Hz, 3H, $-OCH_2-CH_3$), 1.16 (t, *J* = 7.1 Hz, 3H, $-OCH_2-CH_3$). ^{13}C NMR (91 MHz, Chloroform-*d*) δ 157.59, 156.82, 148.74 (d, *J* = 14.3 Hz), 137.26, 129.92 (d, *J* = 30.6 Hz), 126.55, 123.45, 122.52 (d, *J* = 5.1 Hz), 120.35, 119.99, 118.83, 118.44, 118.14 (d, *J* = 5.3 Hz), 113.16, 63.49 (dd, *J* = 16.8, 6.9 Hz), 56.31, 54.64, 16.42 (d, J^3 = 5.8 Hz), 16.24 (d, J^3cp = 5.7 Hz). ^{31}P NMR (162 MHz, Chloroform-*d*) δ 21.54. HRMS (ESI) *m/z* calcd for $C_{24}H_{25}F_3NNaO_4P$ [M^+ Na^+]: 502.1365; Found 400.1343.

2.2.9. Diethyl [benzo [1, 3]dioxol-5-yl((phenylamino)trifluoro-methyl] phosphonate (4i)

Yield: 87%, as white crystalline solid. mp 148.2°C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 8.5 Hz, 2H), 6.97 (s, 1H), 6.95–6.90 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 5.96 (d, *J* = 5.0 Hz, 1H), 5.18 (t, *J* = 8.4 Hz, 1H), 4.69 (dd, *J* = 23.9, 6.6 Hz, 1H), 4.15 (dq, *J* = 14.3, 7.1 Hz, 2H), 4.07–3.94 (m, 1H), 3.84–3.71 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.88 (d, *J* = 34.5 Hz), 126.50, 121.32 (d, *J* = 6.2 Hz), 120.14 (d, *J* = 34.6 Hz), 113.08, 108.42, 107.98 (d, *J* = 4.2 Hz), 101.25, 63.56 (d, *J* = 7.0 Hz), 63.28 (d, *J* = 7.0 Hz), 56.14, 54.62, 16.43 (d, J^3cp = 5.6 Hz), 16.27 (d, *J* = 5.5 Hz). ^{31}P NMR (162 MHz, Chloroform-*d*) δ 21.87. HRMS (ESI) *m/z* calcd for $C_{19}H_{21}F_3NNaO_5P$ [M^+ Na^+]: 454.1001; Found 454.0991.

2.3. Experimental design

A statistical approach was chosen to optimize the synthesis reaction of *α*-aminophosphonates using diphenylphosphinic acid as a new and efficient catalyst under green conditions. A full factorial model of two levels with three operating factors was selected in a first approach (2^3), and each factor takes two

values including a low and high level. Table 1 shows the selected operating factors and their levels in the experiment. All synthesis experiments were realized with three repetitions at the central point ($C_{(P)}$).

Table 1
Coded levels for independent variables were used in the Full Factorial Design (2^3-FFD) Experiments.

Operating Factors	Units	Symbols	Lower Level	Center point	Higher Level
			(-1)	(0)	(+1)
Catalyst amount	mol %	Q_{Cat}	5	10	15
Reaction time	min	t	15	30	60
Medium temperature	°C	T°	25	40	50

The chemical yield (R%) was chosen as the answer (*y*) to achieve the optimal conditions of the synthesis reaction of *α*-aminophosphonates. Data analyzes were performed using statistical software (Minitab18), which allows us to determine the main effects and the interactions between the factors tested. In this study, the total number of experiments (E^{nbr}) performed is reported as follows:

$$\mathrm{E}^{\mathrm{nbr}} = 2^{\beta} + \mathrm{C}_{(\mathrm{p})} \quad (1)$$

Where β is the number of operating factors, and $C_{(p)}$ symbolizes the number of center points used to test for quadratic terms between low and high levels; these central points are used to estimate the clarity and curving of the applied model. So, eleven (11) experiments were conducted in this investigation, including a combination of the factor levels studied. The results of the factorial design, given in terms of the theoretical response (*y*) and a regression model, can be expressed by Eq. (2):

$$= \delta_0 + \sum_{\mathrm{i}=1}^{4} \delta_{\mathrm{i}} \mathrm{x}_{\mathrm{i}} + \sum_{\mathrm{i}=1}^{3} \sum_{\mathrm{j}=\mathrm{i}+1}^{4} \delta_{\mathrm{ij}} \mathrm{x}_{\mathrm{i}} \mathrm{x}_{\mathrm{j}} + \sum_{\mathrm{i}=1}^{2} \sum_{\mathrm{j}=\mathrm{i}+1}^{3} \sum_{\mathrm{k}=\mathrm{j}+1}^{4} \delta_{\mathrm{ijk}} \mathrm{x}_{\mathrm{i}} \mathrm{x}_{\mathrm{j}} \mathrm{x}_{\mathrm{k}} \quad (2)$$

Where δ_0 is the result average value; δ_1, δ_2, *and* δ_3 correspond to the linear coefficients; and δ_{12}, α_{13}, δ_{23}, *and* δ_{123} interaction coefficients between the operating factors and η means the residual term. The symbols Q_{Cat}, *t* and *T°* symbolize the tested variables in the model.

3. Results And Discussion

The synthesis of diethyl *α*-aminophosphonate compounds is realized *by* multi-components *Kabachnik–Fields* reaction. For that, we have chosen the condensation in one pot of aromatic aldehyde (115 mg, 1 mmol), aniline (99 mg, 1 mmol), and diethylphosphite (136 mg, 1.2 mmol) as reaction models.

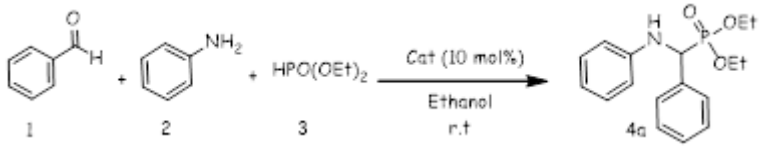
3.1. Organocatalyts screening:

First, the multi-component reaction was performed without catalyst in ethanol, no progress of reaction was observed after 24 h even by increasing the temperature up to 50°C (Table 2, entry 1). We tested different kinds of organocatalyst; *Brønsted acids* such as (*S, S*)-1-oxo-1-hydroxy-2-c,5-*t*-diphenylphospholane (A), 1,1'-binaphtyl-2,2'-dihydrogene-phosphate (B), diphenyl-phosphinic acid (C) and diphenylphosphate acid (D), prolines derivatives such as *N-tert*-butylpyrrolidine-2-carboxamide (E) and *N*-(2-trifluoroacetyl) pyrrolidine-2-carboxamide (F), and Schiff base such as (*E*)-1-(2-hydroxy-5-methoxybenzylidene-amino)-2,3-dihydro-1H-inden-2-ol (G) (Fig. 1). The catalysts screening was made with 10 mol% in ethanol at room temperature within 6 h.

The high activity of (A) and (C) can be attributed to their relative lower acidity compare to (B) and (D). Owing to the commercial availability at low cost of the organocatalyst (C) compared to the tedious preparation steps of the (A) [44–45], the first one is chosen as the best one for the rest of our present investigation.

Unfortunately, the proline derivatives show lower reactivities, the use of the amido proline (E) and trifluoroacetoxy amido proline (F) furnishe the *α*- aminophosphonate 4a with 38% and 11% yieldsrespectively (Table 2, entries 6 and 7). These results are probably due to the high acidity (E) and (F), exhibited by their electron-withdrawing effects. While a problem of the low solubility of the Schiff base (G) still the main cause for no progress of the reaction (Table 2, entry 8).

Table 2
Test of Organocatalysts for the synthesis of α-aminophosphonate **4a**.



Entry	Organocatalyst (10 mol%)	Yield (%)[c]
1[a]	–	–
2[b]	A	92
3	B	75
4	C	93
5	D	78
6	E	38
7	F	11
8	G	Trace

[a] Reaction conditions: aldehyde (1 mmol), aniline (1 mmol) and diethylphosphite (1.2 mmol) were stirred without catalyst in ethanol (2 mL), at 25°C, within 24 h. [b] Reaction conditions: aldehyde (1 mmol), aniline (1 mmol), and diethylphosphite (1.2 mmol) were stirred with the catalyst in ethanol (2 mL) at 25°C within 6 h. [c] Yield of the pure product purified by crystallization in hexane.

3.2. Modeling and optimization of α-aminophosphonates synthesis

Full factorial optimization of the synthesis of *α*-aminophosphonates was performed as a matrix of 11 experiments under the influence of three operating factors with different levels, as shown in Table 3. The results obtained show that the chemical yield ($R_{\%}$) varied from 20–90%; this vast experimental zone can be seen as an improvement for this behavior as it could include the required optimal conditions. The normal probability plot, Pareto plot, surface plots, individual/interaction effects, and optimization plots of the fitted values were examined. Analysis of variance and *p*-value significance levels were estimated to verify the significance of the effect of operating factors on chemical yield. After discarding insignificant terms (i.e Q_{cat}*T°*t), the resulting model was reduced to determine all workable terms ($Q_{cat,}$ T° and t).

Table 3

Reaction conditions applied in Full Factorial Design (2^3-FFD) experiments for the synthesis of *α*-aminophosphonates under green conditions.

Run number	Operating factors			Chemical yields	
	t (min)	Q_{cat} (%)	T (°C)	R_{Exp} (%)	R_{Pred} (%)
1	15	5	25	20.00	22.25
2	60	5	25	40.00	37.75
3	15	15	25	68.00	65.75
4	60	15	25	70.00	72.25
5	15	5	50	50.00	47.75
6	60	5	50	60.00	62.25
7	15	15	50	78.00	80.25
8	60	15	50	88.00	85.75
9	30	10	40	90.00	90.00
10	30	10	40	90.00	90.00
11	30	10	40	90.00	90.00

The ANOVA test was used to determine the significant effect of operating factors and their interactions on chemical yield (R%). Table 4 shows the F-ratio, P-value, sum of squares and mean square of each parameter. Data rank can be judged by its P-value, with values earlier than zero denoting greater significance. The *p*-value should be less than or equal to 0.05 to examine statistical significance with up to a 95% confidence level. In the case of the adopted model, the statistical treatment generated p-values and *F*-values (probability > *F*, indicating the insignificant probabilities), and therefore one could establish the significance of each variable. The variable under study could be more significant when the absolute *F*-value became greater and the *p*-value became lesser. Statistical testing of this model was performed using Fisher's statistical test or Student's t-test for analysis of variance. Accordingly, the quadratic regression shows that the assumed model had a very large *F*-value, on the order of 57.04, indicating a height signification of the model. The analysis of the experimental data indicates that more than 99% of the obtained data can be well predicted by the adopted model with an R^2 reaching 99.25% and R^2_{adj} of 97.51%, indicating that the terms included in recommended model have been measured remarkably enough to make satisfactory predictions.

This section aimed to define the optimal condition for maximum chemical yields of the synthesis of *α*-aminophosphonates. The correctness of the model is confirmed by comparing the experimental data as function of the predicted responses generated by the adopted model. The results obtained showed good agreement between the experimental chemical yields and the predicted values. The predicted response of the model was consistent with the experimental data. In this study, the influence of five independent factors on the response function was examined by a full factorial design to determine the optimal conditions.

Table 4
ANOVA test for quadratic models for the synthesis of *α*-aminophosphonates under green conditions.

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	7	5390.05	770.01	57.04	0.003
Linear	3	3225.50	1075.17	79.64	0.002
t	1	220.50	220.50	16.33	0.027
Q cat	1	2244.50	2244.50	166.26	0.001
T°	1	760.50	760.50	56.33	0.005
2-Way Interactions	3	101.50	33.83	2.51	0.235
t*Q cat	1	40.50	40.50	3.00	0.182
t*T°	1	0.50	0.50	0.04	0.860
Q cat*T°	1	60.50	60.50	4.48	0.125
Curvature	1	2063.05	2063.05	152.82	0.001
Error	3	40.50	13.50		
S	**R-sq**	**R-sq(adj)**			
3.67423	99.25%	97.51%			

In this study, the influence of five independent factors on the response function was examined by a full factorial design to determine the optimal conditions. The mathematical relationship between five important variables and the response can be estimated by a quadratic polynomial equation (Eq. 3):

$$R_{\%}=59{,}25 + 5{,}25\ t + 16{,}75\ Q_{cat} + 9{,}75\ T° - 2{,}25\ t*Q_{cat} - 0{,}25\ t*T° - 2{,}75\ Q_{cat}*T° + 30{,}75\ Ct\ Pt \quad (3)$$

The statistical data of the selected significant model terms are summarized in Table 3 to describe the chemical yields as a function of the operating parameters tested.

3.4. Main individual effects

The individual effects of each operational factor on the chemical yields of the synthesis of *α*-aminophosphonates under green conditions are summarized in Fig. 9. According to the results obtained, we found that the amount of catalyst (Q_{Cat}) has a highly positive effect, which is essentially due to the good catalytic performance and high reactivity of diphenylphosphinic acid **C**, reinforced by its *pKa* values (2.30) as a *Brønsted* acid catalyst compared with the Pka of **A** and phosphoric acid **B** and **D** (3.3, 3.37 and 3.7) respectively. Also, the reaction time (t) and temperature (T°) have a medium positive effect, while the other terms were not significant, with a p-value higher than 0.05 as shown in the Pareto chart (Fig. 3) and Table 4. These results showed good agreement between the predicted and experimental values for

the chemical yields as summarized in Table 3, the main reaction factors were the catalyst amount (Q_{Cat}) with an effect of 33.50 > medium temperature effect (19.50) > the effect of reaction time (10.50).

3.5. Interaction effects between operating factors

The interaction effects between the investigated operating factors are shown in Fig. 4. The interactions between Q_{cat}/T° and t/ Q_{cat} are the most significant with a negative effect of -5.5 and − 4.5 respectively, which is confirmed by the non-parallel borders of the effects. Therefore, the interactions between reaction time (t) and medium temperature effect represented an insignificant effect, which is confirmed by limits, which are easily found at P values less than 0.05, this phenomenon can be explained by the absence of a synergetic effect between these operating factors.

3.6. Determination of optimum conditions

In our study, the main optimization goal was to determine the ideal conditions for the synthesis of *α*-aminophosphonates using diphenylphosphinic acid as an efficient organocatalyst. The request-target was the synthesis of *α*-aminophosphonates in their maximum values in a minimum time in order to obtain the high chemical yield. The obtained results indicated that the highest chemical yield $R_{\%Exp}$ (90.00%) was achieved when each factor value was placed at the optimal level, which is in good agreement with the predicted chemical yield $R_{\%pred}$ (93.51%). Figure 5 exhibits the 3D surface plots of chemical yield evolution as a function of *Qcat/T°* and *t /Qcat* for the synthesis of *α*-aminophosphonates. As can be observed, the chemical yields (R%) highly increase with the increasing amount of diphenylphosphinic acid, at the same time, this phenomenon can be explained by the interaction between the effects of the studied factors.

The best chemical yields of the *α*-aminophosphonate synthesis were obtained under optimum conditions are shown in Table 5. It is anticipated that this behavior may open the way to applying this model for the synthesis of a matrix of MCRs on a series of variously substituted aromatic aldehydes and anilines with electron-withdrawing and electron-donating groups.

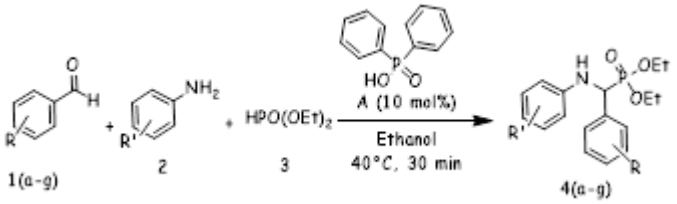
Table 5
Optimum conditions for the synthesis of α-aminophosphonates using diphenylphosphinic acid as an efficient organocatalyst.

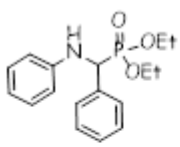
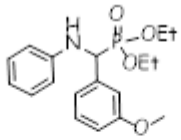
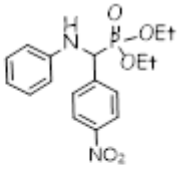
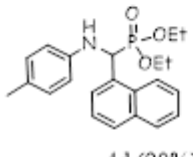
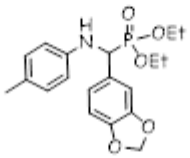
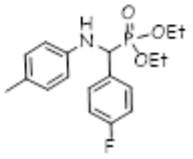
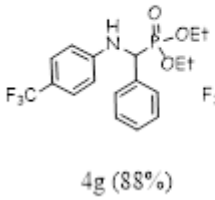
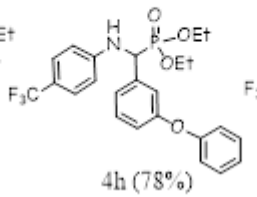
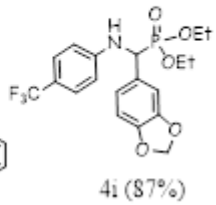
Operating Factors	Symbole	Optimums Values
Reaction time	t	30 min
Catalyst amount	Q_{cat}	10 mol %
Medium temperature	T°	40°C
Predicted chemical yield	R % $_{Pre}$	90.00%
Experimental chemical yield	R % $_{Exp}$	93.51%

3.7. Applied of the optimal conditions:

Based on the optimal conditions of the factorial experiments study, we have investigated the effectiveness and limitations of the MCRs on a series of variously substituted aromatic aldehydes and anilines with electron-withdrawing and electron-donating groups. The reaction proceeds in the presence of diphenylphosphinic acid (10 mol %) in ethanol at 40°C within 30 minutes. The results summarized in Table 6 showed the high efficiency of diphenylphosphinic acid as *Brønsted* catalyst in *Kabachnik-Fields* reaction. The use of aniline with benzaldehyde, 3-methoxybenzaldehyde, and 4-nitrobenzaldehyde leads to the *α*-aminophosphonates **4a**, **4b** and **4c** respectively with excellent chemical yields (up to 90%). Similarly in the presence of toluidine with 1-naphtylbenzaldehyde, dioxobenzaldehyde and 4-fluorobenzldehyde, the **4d**, **4e** and **4f** are obtained in excellent yields (90%, 91% and 80%) respectively. The methyl-trifluoro aniline partially decreases the nucleophilicity of aniline giving the desired products **4g, 4h** and **4i** with **88, 78** and **87%** respectively.

Table 6. Diphenylphosphinic acid catalyzed α-aminophosphonates synthesis.[a]



Product **4** (yield)[b]
 4a (92%)
 4b (98%)
 4c (90%)
 4d (90%)
 4e (91%)
 4f (80%)
 4g (88%)
 4h (78%)
 4i (87%)

[a] Reaction conditions: benzaldehyde (1 mmol), aniline (1mmol) and diethylphosphite (1.2 mmol), Ethanol (2ml), diphenylphosphinic acid (10 mol %), 40°C, 30 min. [b] Yield of the pure product, purified by crystallization from hexane.

According to the obtained results, we propose a mechanism for the synthesis of *α*-aminophosphonates *via* multicomponent condensation reaction in one pot of aromatic aldehyde, aniline and diethylphosphite catalyzed by a diphenylphosphinic acid. At the first time we proposed the coordination of the catalyst and the carbonyl of aromatic aldehyde by hydrogen bond which promotes the attack of the aromatic amine to form the corresponding imine. The diphenylphosphinic acid active again the imine for facilitate the nucleophilic attack of the diethylphosphite which leads to the formation of the desired *α*-aminophosphonates.

4. Conclusion

In conclusion, we have described a novel and highly efficient protocol for the synthesis of *α*-aminophosphonates *via* multicomponent condensation reaction under green conditions, using diphenylphosphinic acid as Bronsted acid and eco-compatible organocatalyst. The full factorial experiment design was successfully used to establish the optimal conditions for optimizing the reaction yield. The regression analysis showed a good correlation between the obtained reaction yields ($R\%_{Exp}$) and predicted yields ($R\%_{Pred}$), which confirmed the validity and practicability of the model, with high and significant R^2 values up to 99.25%%. The static treatment indicated that the diphenylphosphonic acid amount, reaction time, and medium temperature have high signification positive effects on the *α*-aminophosphonates synthesis. The application of the optimization conditions on a series of variously substituted aromatic aldehydes and aromatic amines with electron-withdrawing and electron-donating groups shows the effectiveness of this catalyst gives the *α*-aminophosphonates in excellent to good chemical yields.

Declarations

Ethical Approval

Not applicable

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

All authors contributed to this manuscript. Meriem Ferrah: Synthesis of molecules. Guezane Lakoud Samia: wrote, conceived and designed the study and Methodology, Bendffal Hacene: Wrote and designed the full factorial experiment. Rym AISSA: Investigation. Mounia MERABET-KHELASSI: wrote and investigated Martial TOFFANO: performed the data analysis and wrote this manuscript. Louisa ARIBI-ZOUIOUECHE: wrote and revised.

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Availability of data and materials

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Figures

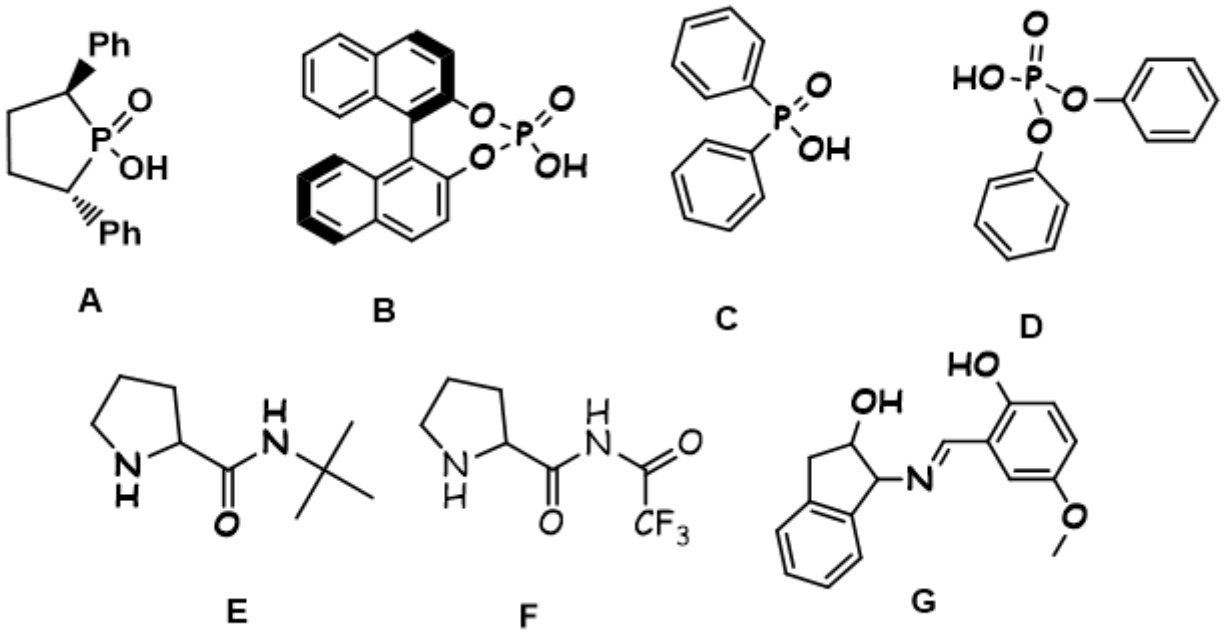

Figure 1

Organocatalysts tested

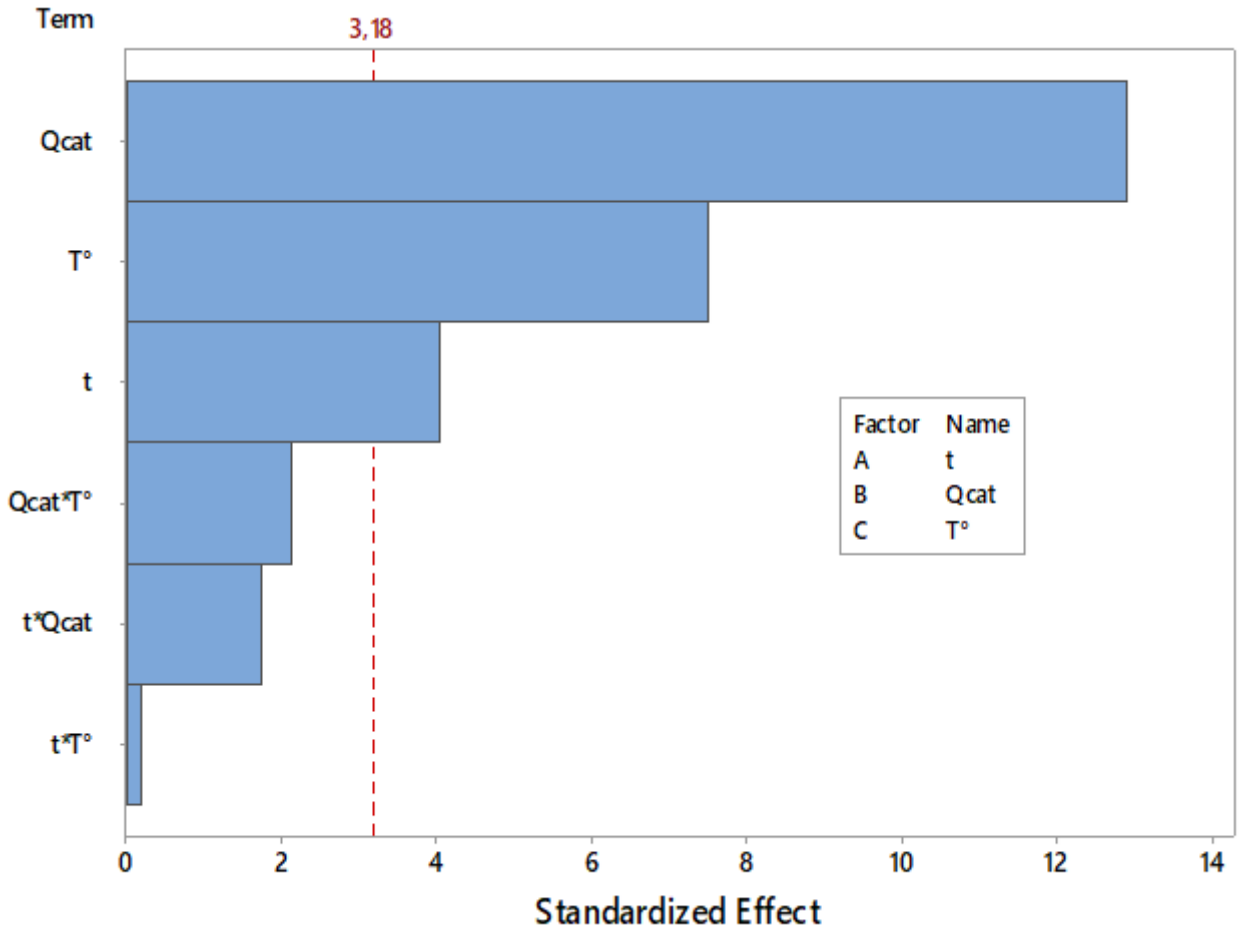

Figure 2

Pareto chart including the effect of each factor on the chemical yields of the synthesis of *α*-aminophosphonates using diphenylphosphinic acid.

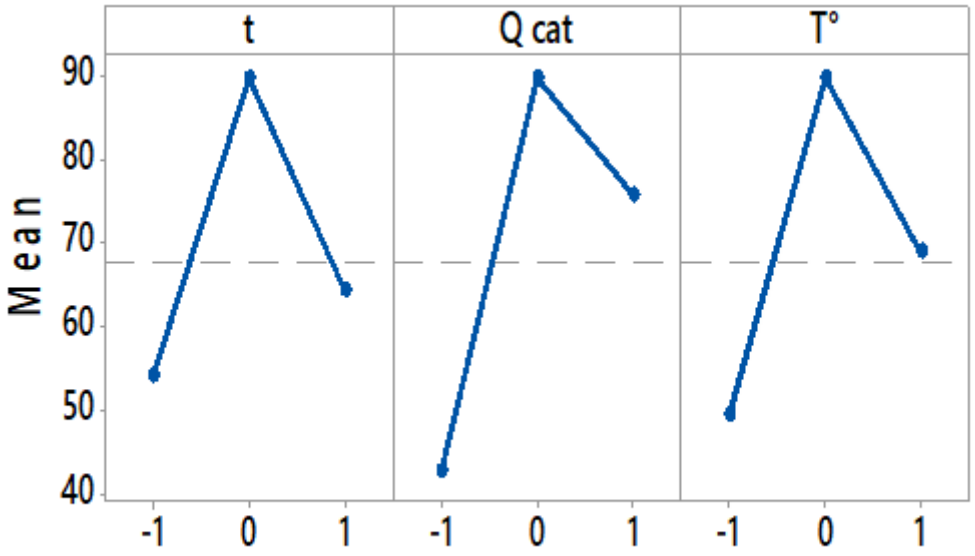

Figure 3

Main effects of the operating factors for the synthesis of *α*-aminophosphonates using diphenylphosphonic acid.

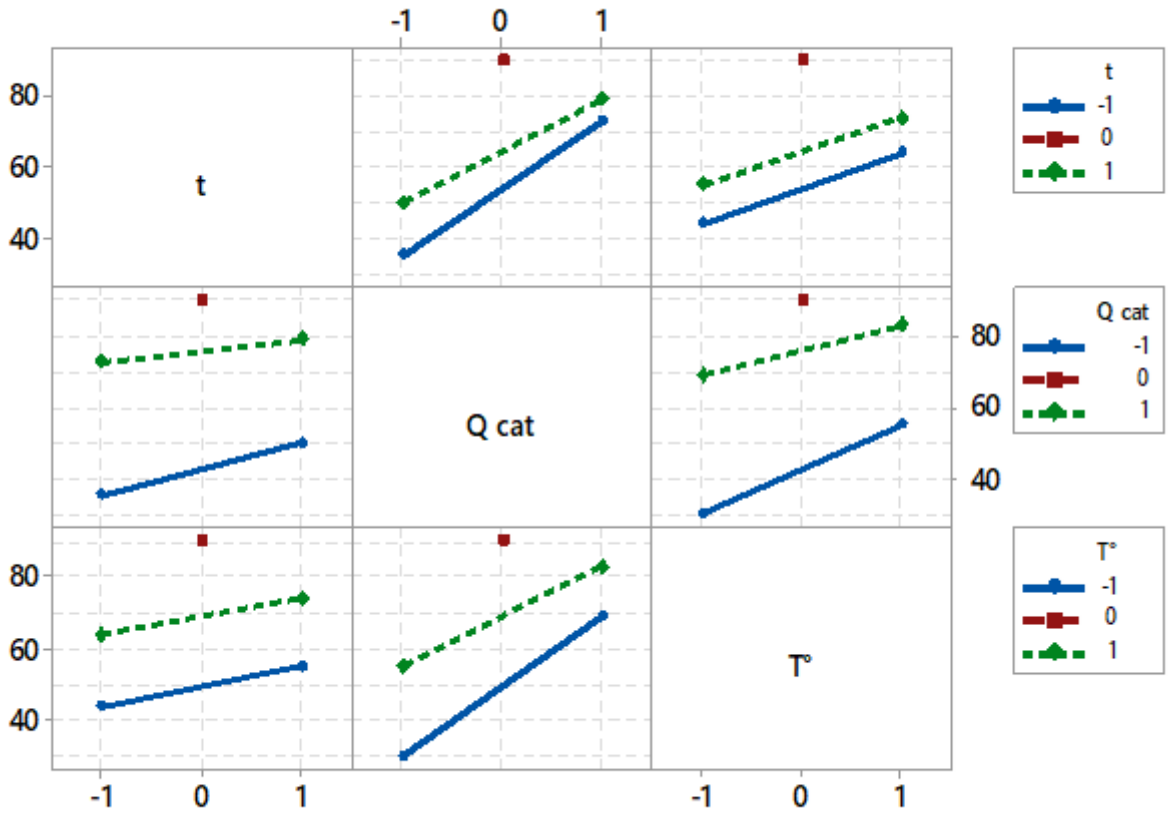

Figure 4

Interactions effects between the operating factors for the synthesis of α-aminophosphonates using diphenylphosphinic acid.

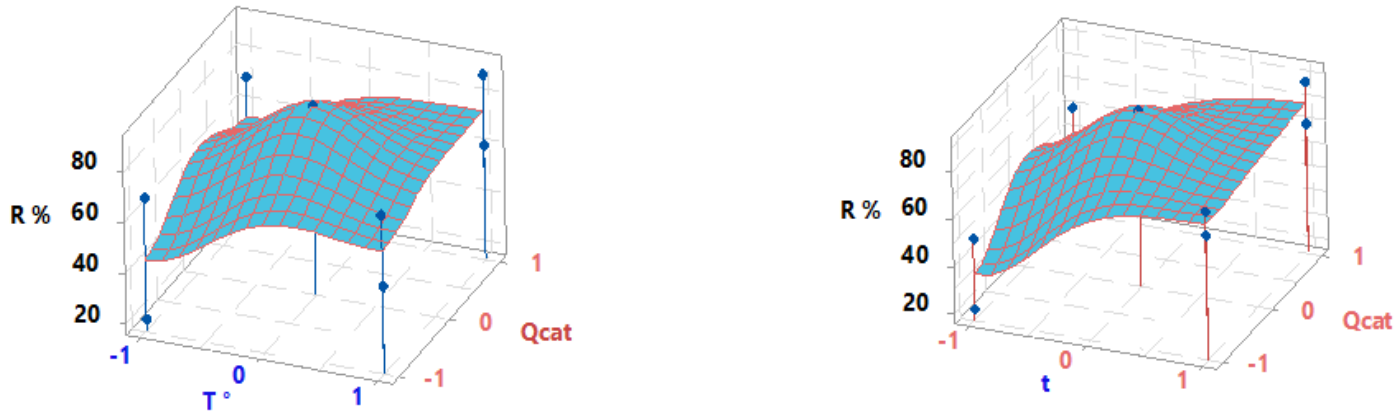

Figure 5

Three-dimensional surface plot of chemical yields as a function of Q_{cat}/T° and t/Q_{cat} for the synthesis of α-aminophosphonates using diphenylphosphinic acid.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Scheme01.png
- SI.docx