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RESEARCH ARTICLE

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Promiscuous lipase catalyzed a new P–C bond formation: Green and efficient protocol for one-pot synthesis of α-aminophosphonates

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Abstract

α-Aminophosphonates are valuable substructures with important biological and pharmacological properties. Lipase catalytic promiscuity is a new method in the organic synthesis for the preparation of α-aminophosphonates via multicomponent reaction in one pot. This efficient, simple, and eco-friendly method proceeds in the presence of immobilized *Candida Antarctica* lipase as catalyst under solvent-free conditions at room temperature. The new α-aminophosphonates are synthesized in high yields (up to 96%). Moreover, enzymatic-catalyzed P–C bond formation through a *Kabachnik-Fields* reaction was achieved for the first time.

1 | INTRODUCTION

The α-aminophosphonates are analogs of amino acids and as such are of great interest in organic synthesis because of their biological and pharmacological activities.[1] That is why the synthesis of new aminophosphonates is underway to find antibiotics,[2] enzymes inhibitors,[3] antileishmanial,[4] antifungal,[5] or antitumoral compounds.[6] For example, compound **1** showed optimal antiproliferative activity to human tumor cells from colon carcinoma and from malignant tumors of the breast and urinary bladder,[7] compound **2** influenced the antitumor activity,[8] and compound **3** showed moderate activities on both cancerous cells and noncancerous cells[9] (Figure 1).

The synthesis of α-aminophosphonates by multicomponent condensation in one pot according to the *Kabachnik-Fields* reaction[10] is widely described in the literature with a variety of catalysts.[11] We have recently reported $NiSO_4{\cdot}6H_2O$ as a new and efficient catalyst for the synthesis of α-aminophosphonates.[12] However, the use of organometallic catalysts does not satisfy us with the objective to develop biologically active compounds through a greener process.

During the three last decades, enzymes have emerged as a powerful catalytic tool for organic synthesis especially in pharmaceutical processes since chirality is a key factor in the efficacy of many drugs.[13] Biocatalysis has many benefits in the context of green and sustainable chemistry as illustrated in the synthesis of active pharmaceutical molecules.[14] The high selectivity of hydrolases as biocatalysts strongly contributes to their use of chiral chemicals synthesis which demand is growing.[15] Lipases are the most used enzymes in synthetic organic chemistry. They allow the development of a practical and environmentally friendly alternative to traditional metallo- and organocatalysis.[16]

More recently, the use of lipases was extended to *catalytic promiscuity* to promote new reactions.[17a] Enzymatic promiscuity is the ability of an enzyme active site to catalyze several different chemical transformations. This has implications not only for fundamental understanding of molecular recognition and evolution of protein function over time but also for the realm of biotechnology.[18] Exploiting enzyme catalytic promiscuity provides new catalytic tools

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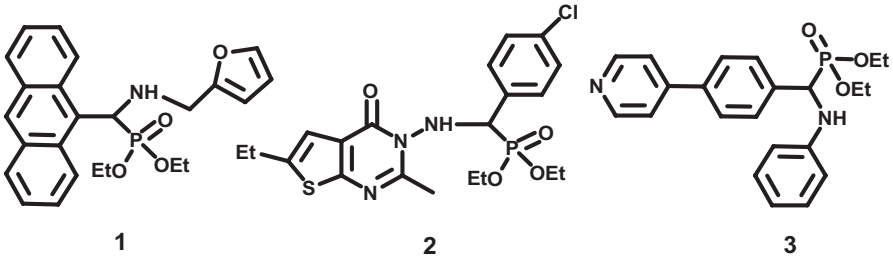


FIGURE 1 Several α-aminophosphonates having biological activities

especially for multicomponent reactions (MCRs). These one-pot reactions allow the creation of several bonds in one step with excellent chemical yields, reduction in reaction times and waste, toward the access to biologically important compounds.[19] Many reactions were successfully revisited, such as the *Mannich* reaction,[20] *Morita-Baylis-Hillman* reaction,[21] *Knoevenagel* reaction,[22] *Henry* reaction,[23] *Michael* addition,[24] and aldolization reaction.[17e]

Lipases are a powerful tool to the organic chemist due to their easy use and many advantages showing broad versatility regarding their catalytic behavior.[25] In our group, the biocatalyst was mostly used in enantioselective catalysis[26] and for the first time, we envisaged lipases to give access to α-aminophosphonates forming a P–C bond by enzymatic promiscuity. Numerous works have shown that lipases are efficient to catalyze in the kinetic resolution of the hydroxyphosphonates.[27]

In the current work, we reported three-component *Kabachnik-Fields* reaction (MCRs) carried out in "one pot" in the presence of a lipase as catalyst to synthesize α-aminophosphonates (Scheme 1).

The reaction is carried out under most environmentally benign reaction conditions due to their enzymatic promiscuity at room temperature and without solvent. To the best of our knowledge, the lipase catalytic promiscuity in the P-C bond-forming reactions has not been reported yet.

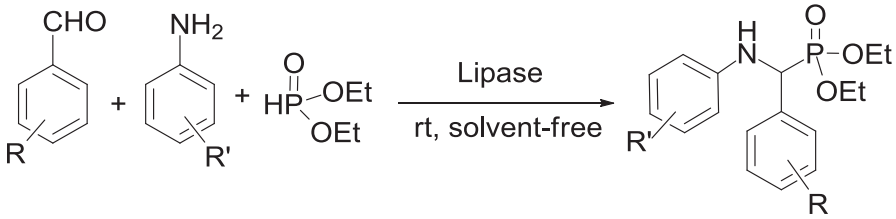
2 | RESULTS AND DISCUSSION

In our quest for developing a lipase-catalyzed MCRs protocol, we selected the reaction of benzaldehyde, aniline, and diethylphosphite as model reaction. We studied several parameters to optimize the reaction conditions such as the lipase nature, the solvent effect, and the reaction time. Four lipases are used, in which three are microbial lipases, Pseudomonas cepacia lipase (*PCL*), *Candida cylindracea* lipase (*CCL*), and *Candida antarctica B* lipase immobilized on acrylic resin (*CAL-B*), and the fourth is animal lipase, *Porcine pancreatic* lipase (*PPL*).

At first, all these lipases are used with a catalytic amount based on the previous work from our laboratory: *PCL* (80 mg), *CCL* (100 mg), *CAL-B* (100 mg), and *PPL* (100 mg). Four different solvents hydrophobicity were studied. The reaction is carried out at 25°C at different reaction times. The results are reported in Table 1.

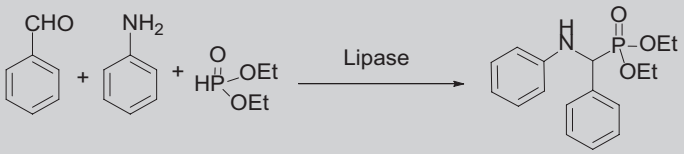
Several commercially available lipases were examined in THF as solvent. For free lipases, *PCL*, *CCL,* and *PPL,* the yield does not exceed 10% (Table 1, entries 1, 2, 3) despite heating at 40°C for 24 hours in THF. Only the *CAL-B* is able to promote the multicomponent reaction in one pot in THF at 40°C (Table 1, entry 4), and the α-aminophosphonate **4a** is obtained in 75% yield. So, the optimum catalytic amount is 50 mg of *CAL-B* (Table 1, entry 5), and using 100 mg of *CAL-B* did not change the yield (Table 1, entry 4 vs entry 5). The reduction in the catalytic amount of the *CAL-B* to 25 mg caused a decrease in yield to 30% with better conditions reaction (Table 1, entry 6 vs entry 5). Then, the study of the multicomponent reaction in various other solvents such as toluene, *diethyl* ether, and methyl *tert*-butyl ether (MTBE) showed a decrease in the yield in **4a** compared to reaction in THF. We obtained a 50% yield in toluene and MTBE (Table 1, entries 7, 8) and 35% yield in ether (entry 9), while in THF, the yield is 75% (entry 5) under the same condition reactions. The desired product was easily obtained by recrystallization from hexane after a simple extraction.

To our delight, the α-aminophosphonate **4a** was obtained in 94% yield exclusively under solvent-free conditions at room temperature by catalytic promiscuity in the presence of 50 mg of *CAL-B* (Table 1, entry 10). Furthermore, there



SCHEME 1 Lipase catalyzed the α-aminophosphonates

TABLE 1 Optimization reaction of the α-aminophosphonates[a,b,c]



Entry	Lipase (mg)	Solvent	*T* (°C)	Time (h)	Yield (%)[c]
1[a]	PCL (80)	THF	40	24	10
2[a]	CCL (100)	THF	40	24	10
3[a]	PPL (100)	THF	40	24	10
4[a]	CAL-B (100)	THF	40	24	75
5[a]	CAL-B (50)	THF	40	24	75
6[a]	CAL-B (25)	THF	40	24	30
7[a]	CAL-B (50)	PhMe	40	24	50
8[a]	CAL-B (50)	TBME	40	24	50
9[a]	CAL-B (50)	Et_2O	40	24	35
10[b]	**CAL-B (50)**	**None**	**25**	**24**	**94**
11[b]	None	None	25	24	NR
12[b]	None	None	40	24	Traces
13[b]	CAL-B (50)	None	25	2	5
14[b]	CAL-B (50)	None	25	6	10
15[b]	CAL-B (50)	None	25	36	94
16[b]	CAL-B (50)	None	25	72	94

The bold values indicate the best condition found for this reaction.
[a]Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), and diethylphosphite (1.2 mmol) were stirred with lipase from solvent (2 mL).
[b]Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), and diethylphosphite (1.2 mmol) were stirred with lipase without solvent.
[c]Yield of the pure product, purified by recrystallization from hexane.

is no reaction in the absence of lipase at 25°C and traces of products appear at 40°C (Table 1, entries 11, 12).

The reaction time of the enzyme catalytic promiscuity reaction was also studied. In less than 10 hours, the desired product was obtained in low yield (<10%) (Table 1, entries 13, 14) while the yield did not increase after 24 hour (94%) (Table 1, entries 10, 15 and 16).

Subsequently, the recycling of *CAL-B* was examined on the model reaction. After completion of the reaction, the lipase was removed by filtration, recovered, and reused three times. There is a decrease in catalytic performance for the 3rd cycle (Figure 2).

To validate this new method of biocatalytic promiscuity with *CAL-B* and to show the effectiveness of the MCRs reaction, we applied the optimized reaction on a series of variously substituted aldehydes with electron-withdrawing and electron-donating groups associated with various aromatic amines in order to access to α-aminophosphonates. The results are summarized in Table 2.

The three-component condensation reaction in one pot was carried out among a series of various aromatic aldehyde, different aromatic amines and diethylphosphite with 50 mg

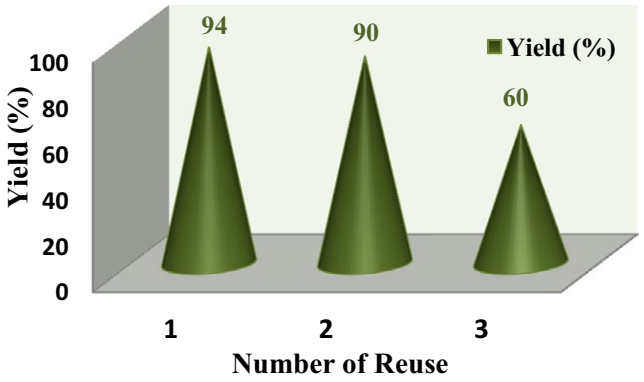
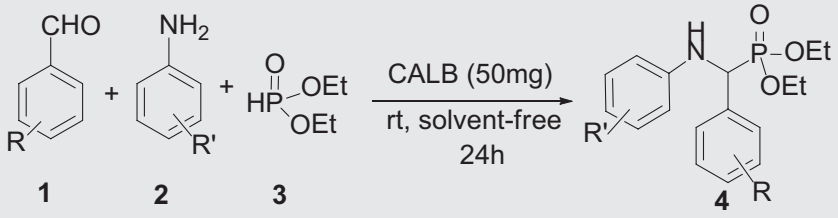


FIGURE 2 Reusing of the *CAL-B* catalyst

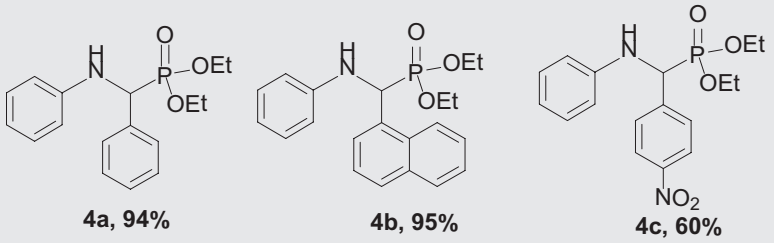
of *CAL-B* without solvent for 24 hours at room temperature. The α-aminophosphonates are obtained in 40%-96% yield depending on the structures of the aldehyde and the amine. We also confirmed the activity of the *CAL-B* after the reaction described and verified that the lipase is not deactivated under the reaction conditions.

Use of aniline with benzaldehyde, 1-naphtaldehyde, and 4-nitrobenzaldehyde leads, respectively, to the

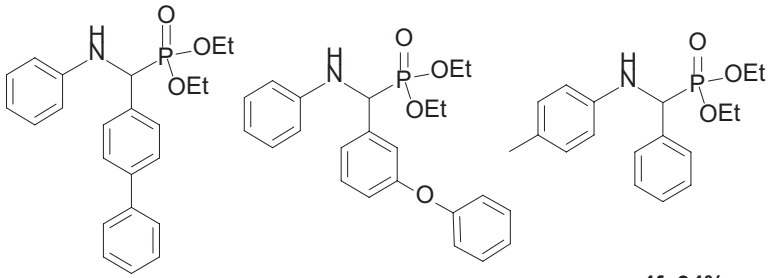
TABLE 2 Lipase-catalyzed synthesis of a series α-aminophosphonates[a,b]



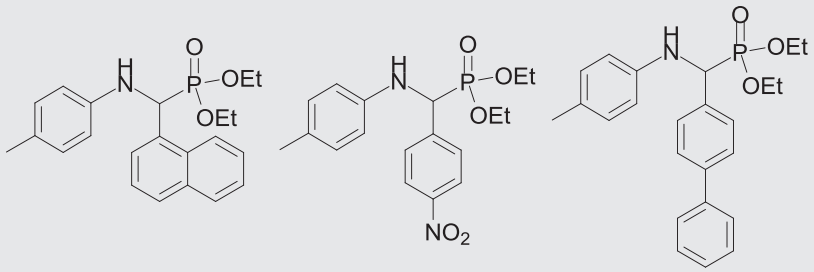
α-aminophosphonates **4(a-o)** (yield %)



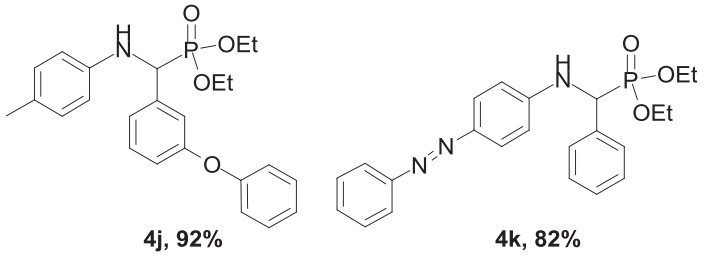
4a, 94% **4b, 95%** **4c, 60%**



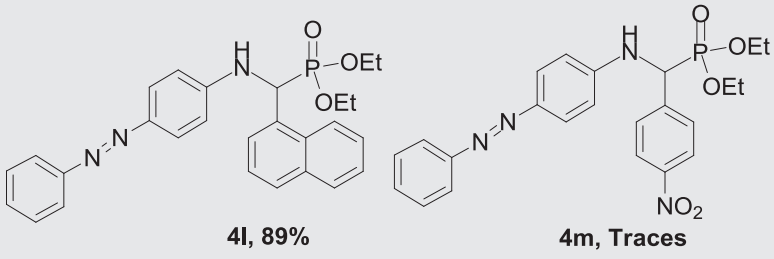
4d, 40% **4e, 90%** **4f, 94%**



4g, 96% **4h, 65%** **4i, 45%**



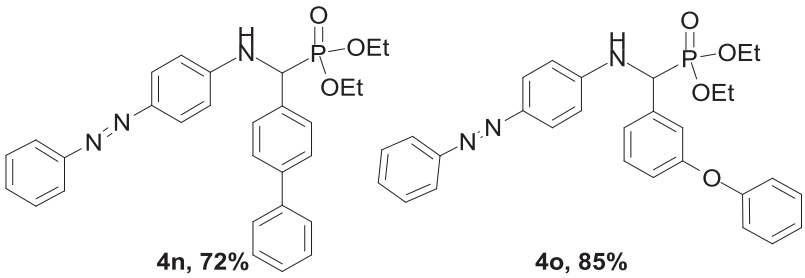
4j, 92% **4k, 82%**



4l, 89% **4m, Traces**

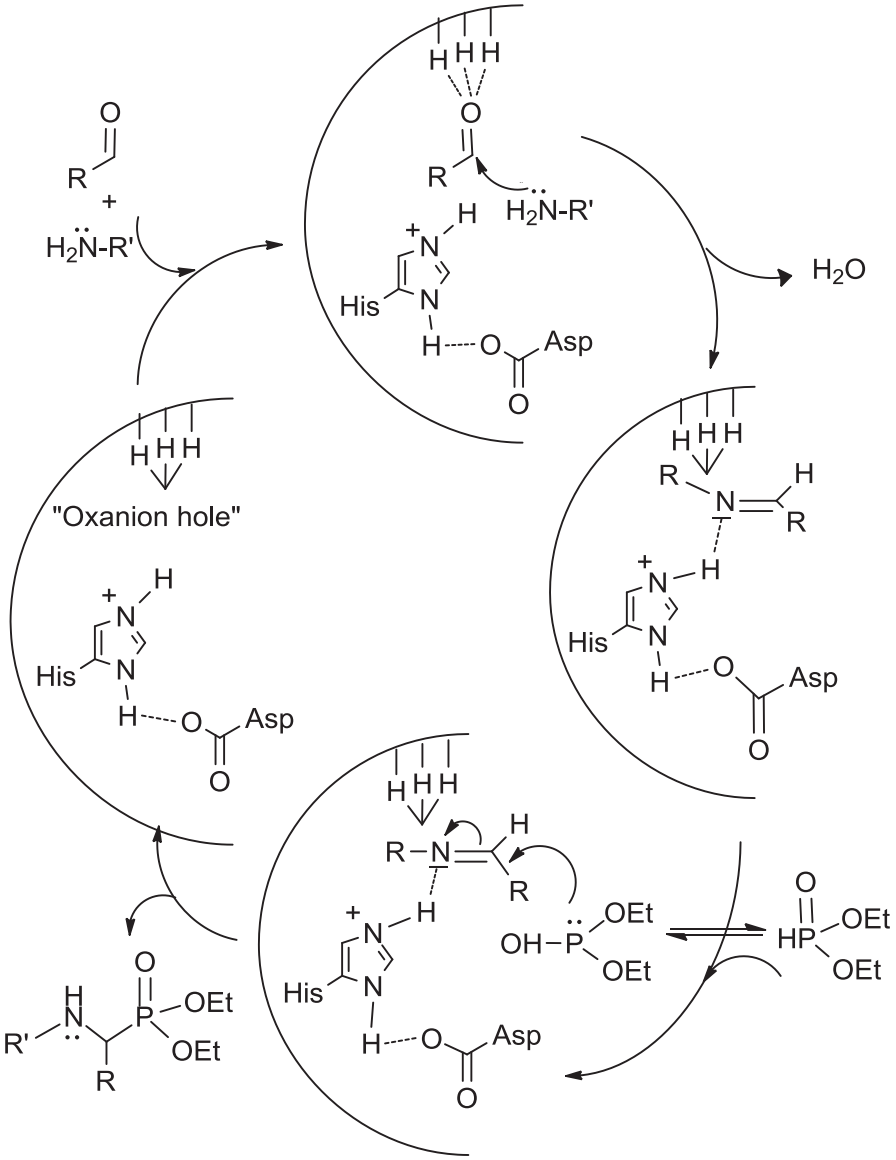
(Continues)

TABLE 2 (Continued)



[a]Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), and diethylphosphite (1.2 mmol), CAL-B (50 mg), room temperature, 24 h.
[b]Yield of the pure product, purified by recrystallization from hexane.

α-aminophosphonates **4a**, **4b,** and **4c** with 60%-95% yield. Similarly in the presence of toluidine with the above series of aromatic aldehydes, the α-aminophosphonates **4f**, **4g**, and **4h** are obtained in 65%-96% yield. The use of 4-biphenylbenzaldehyde with aniline and toluidine gives moderate yields of the α-aminophosphonates **4d** (40%) and **4i** (45%), respectively. The presence of the phenyl in position 4 probably hinders the coordination with the natural active site of the lipase. This phenomenon is reduced with the compound **4n**. This suggests a probably different enzymatic



SCHEME 2 Proposed mechanism of *CAL-B*-catalyzed Kabachnik-Fields reaction

activation mode in the presence of diazo group. Indeed, the use of 4-phenylazoaniline and 3-phenoxybenzaldehyde leads to original α-aminophosphonates structures **4e**, **4j**, **4k**, **4l**, **4n,** and **4o** with excellent yields in the range 72%-92%. This indicates that the effectiveness of the catalytic promiscuity *CAL-B* is provided by aromatic aldehydes substituted electron-donating groups. In the case of 4-nitrobenzaldehyde with phenylazoaniline, the MCRs show only traces of compound **4m**. The absence of reactivity in this case is probably due to the combined effects of the geometry of the molecules with a sterically hindered group associated with the presence of the electron-withdrawing group, which impedes the approach of the active site.

It is interesting to note that all α-aminophosphonates obtained are racemic, and no asymmetric induction is induced by *CAL-B*. The majority of papers on enzymatic promiscuity for carbon–carbon bond-forming reactions that yield chiral products report low or no enantioselectivities despite the fact that enzymes provide a natural chiral environment for asymmetric catalysis.[17f,28] However, the synthesis of α-aminophosphonates is carried out under conditions of MCRs by catalysis with a lipase under solvent-free condition which is a synthetic route including biocatalysis, MCRs, neat reaction, the biocatalyst reuse, simple purification without column chromatography, the criteria for a green chemistry process.[29]

Based on the generally accepted chemically catalyzed mechanism of the *Kabachnik-Fields* reaction[12,30] and the literature regarding enzymatic promiscuity to form carbon–carbon bonds,[17a,c,f] a mechanism was suggested for the C–P bond formation starting the interaction with lipase active site of *CAL-B* (Scheme 2).

The active site of *CAL-B* contains the catalytic triad, Ser105-His224-Asp187 common to all serine hydrolases. The top pocket is the "oxyanion hole." It is a spatial arrangement of three hydrogen-bond donors, one from the side chain of Thr40 and two from the backbone amides of Thr40 and Gln106.[31] When the *CAL-B* catalyzes promiscuous C–C bond formation reactions, the "oxyanion hole" is utilized for negative charge stabilization. It seems that in these reactions, the nucleophilic serine takes no role, and acid-base transfer is thought to be mediated by His 224 in conjunction with Asp187.[32] In this case, the C–P bond is formed by enzymatic proximity by direct *CAL-B*-catalyzed three-component reaction between benzaldehyde, amine, and diethylphosphite.

The formation of the imine is supposed to be the first step of the reaction. The influence of the order of addition of the three components in "one pot" with lipase has been investigated. The multicomponent reaction is carried out in three different protocols: (i) Benzaldehyde, aniline, and *CAL-B* were mixed together for a few minutes, and then, diethylphosphite was added; (ii) benzaldehyde, diethylphosphite, and *CAL-B* were mixed together for a few minutes, and then, aniline was added; (iii) aniline, diethylphosphite, and *CAL-B* were mixed during a few minutes, and then, benzaldehyde was added. It is observed that only the reaction carried out according to the first order was effective and afforded the α-aminophosphonates with an excellent yield (94%). In the case of the two other procedures, the reaction did not proceed. These observations strengthen the initial formation of an imine in the presence of lipase by coordination. In the absence of lipase, the imine was not formed in the reaction conditions.

In this case, the imine is formed rapidly between aromatic benzaldehyde and aromatic amines in coordination with "oxyanion hole" (carbonyl pocket). The lipase active site is activated by a relay of hydrogen bond with histidine, aspartate, and oxygen of aromatic aldehyde which promotes the attack of the aromatic amine and the corresponding imine formation, followed by a nucleophilic attack of the phosphite, which leads to the formation of the P–C bond and the desired α-aminophosphonates.

3 | CONCLUSION

An efficient and simple method for the synthesis of α-aminophosphonates derivatives via *Kabachnik-Fields* reaction catalyzed by *CAL-B* is reported for the first time. After optimization of reaction conditions, all the products could be obtained in high yields (from 45% to 95%). The multicomponent reaction in one pot, aromatic aldehydes, aromatic amines, and diethylphosphite, was achieved in the presence of *CAL-B* (50 mg) at room temperature under solvent-free conditions. Easy purification and the absence of column chromatography are the highlights of the process. The lipase was easily recovered and reused. New α-aminophosphonates **4e**, **4j**, **4k**, **4l**, **4n**, and **4o** have been prepared. This new synthetic route incorporates several green chemistry principles, atom economy, biocatalyst, environmental friendliness, and simple operational process. This work significantly expands the utility of *CAL-B* for important carbon–phosphorus bond-forming reactions. These results are starting point for more applications of biocatalysts in organic synthesis.

4 | EXPERIMENTAL SECTION

4.1 | General information

All starting materials and reagents used in this study were obtained commercially from Aldrich and Acros and were used without purification. Various commercially available lipases were screened: lipase from *Porcine pancreas* type II (*PPL*; LA = 100-500 U/mg), *Candida Cylindracea* lipase (*CCL*, LA = 3.85 U/mg), *Pseudomonas Cepacia* lipase (*PCL*; LA > 30 000 U/mg), and the *Candida antarctica* lipase fraction B immobilized on acrylic resin (*CAL-B*; LA > 10 000 U/mg). All 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. ^1H NMR and ^{13}C NMR spectra were recorded with Bruker spectrometers (300 MHz and 250 MHz for ^1H, 75 MHz and 63 MHz for ^{13}C and 101 MHz and 121 MHz for ^{31}P). Chemical shifts were reported downfield from $CDCl_3$ (δ = 7.26 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent of $CDCl_3$ (δ = 77 ppm) used as internal reference. Coupling constants (J) are given in hertz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. Melting points were measured using Büchi Melting Point B-545. Mass spectra were recorded with a MicrOTOF-Q Bruker spectrometer using electrospray ionization (ESI) analysis.

4.2 | General procedure for synthesis of α-aminophosphonates 4a-4o

To the reaction mixture containing aromatic aldehyde **1** (100 mg, 1 mmol), aromatic amine (93 mg, 1 mmol), and diethylphosphite (165 mg, 1.2 mmol), a *CAL-B* (50 mg) was added. It was stirred for an appropriate time at room temperature for 24 hours. After the reaction proceeded to completion, the enzyme was removed by filtration. The filtrate was washed by 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 recrystallization in hexane. Complete experimental data have been provided (NMR spectra and HRMS).

4.2.1 | Diethyl [phenyl(phenylamino)methyl] phosphonate (4a)[11,12]

Yield: 94%, as a white crystalline solid; mp 88°C. ^1H 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.

4.2.2 | Diethyl [1-naphtyl(phenylamino) methyl]phosphonate (4b)[11,12]

Yield: 95%, as a white crystalline solid; mp 123°C. ^1H NMR (250 MHz, $CDCl_3$, 25°C): δ 8.26 (d, 1H, J_{HP} = 8.3 Hz, ArH), 7.89-7.44 (m, 6H, ArH), 7.05-7.02 (dd, 2H, J = 8.5, 7.4 Hz, ArH), 6.68-6.63 (dd, 1H, J = 10.6, 4.1 Hz, ArH), 6.57-6.53 (m, 2H, ArH), 5.60 (d, 1H, J_{HP} = 24.1 Hz, CHP), 5.10 (s, 1H, NH), 4.25-4.13 (m, 2H, $OCH_2–CH_3$), 3.75-3.72 (m, 1H, $–OCH_2–CH_3$), 3.25-3.15 (m, 1H, $–OCH_2–CH_3$), 1.33 (t, 3H, J = 7.00 Hz, $–OCH_2–CH_3$), 0.70 (t, 3H, J = 7.1 Hz, $–OCH_2–CH_3$). ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ ^{13}C NMR (63 MHz, $CDCl_3$): δ 146.11 (d, J = 13.9 Hz), 133.81, 131.63 (d, J = 8.0 Hz), 129.09 (d, J = 10.6 Hz), 128.44, 126.25, 126.05, 125.65, 125.37 (d, J = 5.8 Hz), 122.94, 118.26, 113.57, 63.26 (dd, J^2_{CP} = 12.4, 6.8 Hz), 52.67, 50.25, 16.45 (d, J^3_{CP} = 6.2 Hz), 15.75 (d, J^3_{CP} = 5.7 Hz). ^{31}P NMR (101 MHz, $CDCl_3$, 25°C): δ 22.98 ppm. HRMS (ESI) *m/z* calcd for $C_{21}H_{24}NO_3P$ [$M + Na^+$]: 392.1401; Found 392.1386.

4.2.3 | Diethyl [4-nitrophenyl(phenylamino) methyl]phosphonate (4c)[11,12]

Yield: 94%, as a yellow crystalline solid; mp 89.2°C. ^1H NMR (250 MHz, $CDCl_3$, 25°C): δ 8.22-8.19 (m, 2H, ArH), 7.69-7.64 (dd, 2H, J_{HP} = 8.80, 2.3 Hz, ArH), 7. 15-7. 09 (m, 2H, ArH), 6.77-6.71 (t, 2H, J = 7.4 Hz, ArH), 6.59-6.52 (m, 2H, ArH), 4.92-4.81 (d, 1H, J_{HP} = 25.2 Hz, CHP), 4.19-4.10 (m, 2H, $OCH_2–CH_3$), 4.09-4.02 (m, 1H, $–OCH_2–CH_3$), 3. 99-3. 95 (m, 1H, $–OCH_2–CH_3$), 1.30 (t, 3H, J = 7.00 Hz, $–OCH_2–CH_3$), 1.19 (t, 3H, J = 7.1 Hz, $–OCH_2–CH_3$). ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ ^{13}C NMR (63 MHz, $CDCl_3$): δ 147.59, 145.63 (d, J = 14.2 Hz), 144.04 (d, J = 2.5 Hz), 129.34, 128.63 (d, J = 4.9 Hz), 123.75, 119.10, 113.79, 63.60 (dd, J^2= 17.1, 6.9 Hz), 57.20, 54.84, 16.30 (dd, J^3_{CP} = 10.3, 5.5 Hz). ^{31}P NMR (101 MHz, $CDCl_3$, 25°C): δ 21.31 ppm. HRMS (ESI) *m/z* calcd for $C_{17}H_{21}N_2O_5P$ [$M + Na^+$]: 387.1094; Found 387.1080.

4.2.4 | Diethyl [4-biphenyl(phenylamino) methyl]phosphonate (4d)[12]

Yield: 94%, as a white crystalline solid; mp 158°C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64-7.53 (m, 6H, ArH), 7.45 (t, J = 7.4 Hz, 2H, ArH), 7.36 (t, J = 6.7 Hz, 1H, ArH), 7.15 (t, J = 7.9 Hz, 2H, ArH), 6.74 (t, J = 7.3 Hz, 1H, ArH), 6.66 (d, J = 8.1 Hz, 2H, ArH), 4.89 (d, J = 7.5 Hz, 1H, HCP), 4.80 (d, J = 7.7 Hz, 1H, NH), 4.27-4.09 (m, 2H, $–OCH_2–CH_3$), 4.01-3.80 (m, 1H, $–OCH_2–CH_3$), 3.78-3.96 (m, 1H, $–OCH_2–CH_3$), 1.33 (t, J = 7.1 Hz, 3H, $–OCH_2–CH_3$), 1.18 (t, J = 7.1 Hz, 3H, $OCH_2–CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.26 (d, J = 21.3 Hz), 140.70 (d, J = 6.8 Hz), 134.92, 129.22, 128.78, 128.72, 128.23 (d, J = 5.4 Hz), 127.35 (d, J = 2.9 Hz), 127.29, 127.02, 118.48, 113.88, 63.35 (d, J^2_{CP} = 7.0 Hz), 56.81, 54.82, 16.47 (d, J^3_{CP} = 5.8 Hz), 16.25 (d, J^3_{CP} = 6.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 22.58 ppm. HRMS

(ESI) *m/z* calcd for $C_{23}H_{26}NO_3P$ [$M + Na^+$]: 418.1550; Found 418.1542.

4.2.5 | Diethyl [3-phenoxy(phenylamino) methyl]phosphonate (4e)

Yield: 94%, as a white crystalline solid; mp 127°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.26 (m, 4H, ArH), 7.24 (m, 4H, ArH), 6.94 (t, J = 8.5 Hz, 3H, ArH), 6.74 (t, J = 7.3 Hz, 1H, ArH), 6.60 (d, J = 8.3 Hz, 2H, ArH), 4.85-4.68 (m, 2H, HCP + NH), 4.23-4.07 (m, 2H, –OCH_2–CH_3), 4.08-3.94 (m, 1H, –OCH_2–CH_3), 3.88-3.71 (m, 1H, –OCH_2–CH_3), 1.30 (t, J = 7.0 Hz, 3H, –OCH_2–CH_3), 1.18 (t, J = 7.1 Hz, 3H, –OCH_2–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.17 (d, J = 22.5 Hz), 146.15 (d, J = 14.7 Hz), 138.12, 129.90, 129.72, 129.17, 123.26, 122.72 (d, J = 5.0 Hz), 118.47 (dd, J = 20.2, 14.8 Hz), 113.96, 63.31 (d, J^2_{CP} = 10.6 Hz), 56.92, 54.93, 16.43 (d, J^3_{CP} = 5.5 Hz), 16.24 (d, J^3_{CP} = 5.9 Hz). ^{31}P NMR (101 MHz, $CDCl_3$, 25°C): δ 22.26 ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{26}NO_4P$ [$M + Na^+$]: 434.1491; Found 434.1491.

4.2.6 | Diethyl [phenyl(p-tolylamino)methyl] phosphonate (4f)[12]

Yield: 94% as a white crystalline solid; mp 120°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.49-7.47 (m, 2H, ArH), 7.37-7.27 (m, 3H, ArH), 6.93 (d, J = 8.3 Hz, 2H, ArH), 6.53 (d, 2H, J = 8.4 Hz, ArH), 4.76 (d, J = 24.2 Hz, 2H, HCP and NH), 4.17-4.10 (m, 2H, –OCH_2–CH_3), 4.00-3.92 (m, 1H, –OCH_2–CH_3), 3.74-3.66 (m, 1H, –OCH_2–CH_3), 2.20 (s, 3H, CH_3-Ph), 1.30 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3), 1.13 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ ^{13}C NMR (63 MHz, $CDCl_3$) δ 143.95 (d, J = 15.1 Hz), 135.98, 129.62, 128.50, 127.81 (d, J = 4.7 Hz), 127.58, 113.96, 64.83-61.51 (m), 57.54, 55.15, 20.31, 16.27 (dd, J^3_{CP} = 15.2, 5.7 Hz). ^{31}P NMR (101 MHz, $CDCl_3$, 25°C): δ 21.48 ppm. HRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_3P$ [$M + Na^+$]: 356.1397; Found 356.1386.

4.2.7 | Diethyl [1-naphtyl(p-tolylamino) methyl]phosphonate (4g)[11]

Yield: 94%, 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, HCP), 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, 131.68 (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, 20.33, 16.49 (d, J = 5.9 Hz), 15.79 (d, J = 5.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 23.07 ppm. HRMS (ESI) *m/z* calcd for $C_{22}H_{26}NO_3P$ [$M + Na^+$]: 406.1555; Found 406.1542.

4.2.8 | Diethyl [4-nitrophenyl(p-tolylamino) methyl]phosphonate (4h)[12]

Yield: 94%, as a yellow crystalline solid; mp 158°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.21 (d, J = 8.5 Hz, 2H, ArH), 7.67 (dd, J = 8.8, 2.3 Hz, 2H, ArH), 6.94 (d, 2H, J = 8.3 Hz, ArH), 6.46 (d, J = 8.4 Hz, 2H, ArH), 4.85 (d, J = 25.1 Hz, 2H, HCP+NH), 4.20-4.02 (m, 3H, –OCH_2–CH_3), 3.94-3.86 (m, 1H, –OCH_2–CH_3), 2.35 (s, 3H, CH_3-Ph), 1.32 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3), 1.21 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 147.54, 144.20, 143.25 (d, J = 14.8 Hz), 129.86, 128.65 (d, J = 4.8 Hz), 128.62, 123.74, 113.93, 63.58 (dd, J^2_{CP} = 23.8, 6.9 Hz), 57.26, 55.29, 20.36, 16.45 (d, J^3_{CP} = 12.6 Hz), 16.30 (d, J^3_{CP} = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 20.94 ppm. HRMS (ESI) *m/z* calcd for $C_{18}H_{24}N_2O_5P$ [$M + H^+$]: 379.1412; Found 379.1417.

4.2.9 | Diethyl [4-biphenyl(p-tolylamino) methyl]phosphonate (4i)[12]

Yield: 94%, as a white crystalline solid; mp 140°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ 7.42-7.59 (m, 6H, ArH), 7.26-7.39 (m, 3H, ArH), 6.93 (d, 2H, J = 8.2 Hz, ArH), 6.55 (d, 2H, J = 8.4 Hz, ArH), 4.79 (d, 1H, J = 24.3 Hz, HCP), 4.10-4.18 (m, 2H, OCH_2–CH_3), 3.84-4.01 (m, 1H, –OCH_2–CH_3), 3.71-3.81 (m, 1H, –OCH_2–CH_3), 2.19 (s, 3H, CH_3-Ph), 1.30 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3), 1.15 (t, 3H, J = 7.0 Hz, –OCH_2–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 143.82, 140.59, 129.67, 128.70, 128.20 (d, J = 5.5 Hz), 127.66, 127.24 (d, J = 2.7 Hz), 126.96, 113.98, 63.31 (t, J = 7.0 Hz), 57.28, 54.87, 20.33, 16.38 (d, J^3_{CP} = 14.0 Hz), 16.16 (d, J^3_{CP} = 5.5 Hz) ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 22.71 ppm. HRMS (ESI) *m/z* calcd for $C_{24}H_{29}NO_3P$ [$M + H^+$]: 410.1876; Found 410.1879.

4.2.10 | Diethyl [3-phenoxy(p-tolylamino) methyl]phosphonate (4j)

Yield: 94%, as a white crystalline solid; mp 128.5°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 4H), 7.17-7.05 (m, 2H, ArH), 6.95 (dd, J = 10.7, 4.6 Hz, 4H, ArH), 6.51 (d, J = 8.5 Hz, 2H, ArH), 4.73 (d, J = 24.4 Hz, 1H, HCP), 4.21-4.11 (m, 2H, –OCH_2–CH_3), 4.07-3.95 (m, 1H, –OCH_2–CH_3), 3.80-3.76 (m, 1H, –OCH_2–CH_3), 2.22 (s, 3H, $ArCH_3$), 1.30 (t, J = 7.1 Hz, 1H, –OCH_2–CH_3), 1.18 (t, J = 7.1 Hz, 1H, –OCH_2–CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ 157.19 (d, J = 15.9 Hz), 143.82 (d, J = 15.1 Hz), 138.04, 129.88, 129.69, 123.23, 122.73 (d, J = 5.2 Hz), 118.74, 118.55, 114.10, 63.29 (t, J = 7.7 Hz), 57.40, 55.01, 20.36, 16.43 (d, J^3_{CP} = 5.6 Hz), 16.24 (d, J^3_{CP} = 5.7 Hz). ^{31}P NMR: (121 MHz, $CDCl_3$, 25°C): δ 22.38 ppm. HRMS (ESI) m/z calcd for $C_{23}H_{26}NO_4P$ [M + Na^+]: 448.1648; Found 448.1640.

4.2.11 | Diethyl [phenyl(p-phenylazoaniline) methyl]phosphonate (4k)

Yield: 94%, as a grown crystalline solid; mp 114.5°C. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): δ 7.82-7.75 (m, 4H, ArH), 7.50-7.26 (m, 8H, ArH), 6.68 (d, J = 8.9 Hz, 2H, ArH), 5.32 (s, J = 24.7, 1H, NH), 4.85 (d, J = 24.1 Hz, 1H, CH), 4.19-4.12 (m, 2H, –OCH_2–CH_3), 4.10-3.89 (m, 1H, –OCH_2–CH_3), 3.70-3.60 (m, 1H, –OCH_2–CH_3), 1.32 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3), 1.12 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3). ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.29, 152.96, 148.97 (d, J = 19.8 Hz), 145.47, 135.28, 129.74, 128.92, 128.75, 128.21, 127.79 (d, J = 5.3 Hz), 124.92, 122.29, 63.54 (d, J^2_{CP} = 7.1 Hz), 63.29 (d, J^2_{CP} = 6.9 Hz), 56.99, 54.59, 16.41 (d, J^3_{CP} = 6.0 Hz), 16.15 (d, J^3_{CP} = 5.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 22.05 ppm. HRMS (ESI) m/z calcd for $C_{23}H_{26}N_3O_3P$ [M + H^+]: 424.1785; Found 424.1784.

4.2.12 | Diethyl [naphtyl(p-phenylazoaniline)methyl]phosphonate (4l)

Yield: 94%, as a grown crystalline solid; mp 131.5°C. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C): δ 8.26 (d, J = 8.4 Hz, 1H, ArH), 7.80-7.69 (m, 9H, ArH), 7.49-7.26 (m, 4H, ArH), 6.64 (d, J = 8.9 Hz, 2H, ArH), 5.73 (d, J = 23.8 Hz, 1H, CH), 4. 27-4.16 (m, 2H, –OCH_2–CH_3), 3.76-3.72 (m, 1H, OCH_2–CH_3), 3.24-3.14 (m, 1H, OCH_2–CH_3), 1.35 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3), 0.73 (t, 3H, J = 7.0 Hz, OCH_2–CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ 152.91, 148.87 (d, J = 13.2 Hz), 145.28, 133.84, 131.18 (d, J = 24.2 Hz), 129.67, 129.11, 128.99 (d, J = 15.6 Hz), 126.49, 125.82, 125.59, 124.97, 122.73, 122.25, 113.32, 63.64 (d, J = 6.9 Hz), 63.25 (d, J = 7.2 Hz), 52.57, 50.15, 16.47 (d, J = 5.2 Hz), 15.74 (d, J = 5.6 Hz). ^{31}P NMR (101 MHz, $CDCl_3$, 25°C): δ 21.91 ppm. HRMS (ESI) m/z calcd for $C_{27}H_{28}N_3O_3P$ [M + Na^+]: 496.1749; Found 496.1760.

4.2.13 | Diethyl [4-biphenyl(p-phenylazoaniline)methyl] phosphonate (4n)

Yield: 94%, as a grown crystalline solid; mp 132.5°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.83 (d, J = 13.84 Hz, 1H, ArH), 7.50-6.99 (m, 11H, ArH), 6.70 (d, J = 8.7 Hz, 2H, ArH), 5. 37 (t, J = 23.8 Hz, 1H, CH), 4.86 (dd, J = 24.2, 7.8 Hz, 1H), 4.22-4.14 (m, 2H, –OCH_2–CH_3), 4.12-4.00 (m, 1H, –OCH_2–CH_3), 3.85-3.77 (m, 1H, –OCH_2–CH_3), 1.33 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3), 1.20 (t, 3H, J = 7.1 Hz, –OCH_2–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.55, 156.88, 152.98, 148.94 (d, J = 13.7 Hz), 145.54, 137.55, 130.09, 129.81, 128.99, 124.94, 123.45, 122.63 (d, J = 4.7 Hz), 122.35, 118.87, 118.44, 118.28 (d, J = 5.3 Hz), 113.64, 63.52 (dd, J = 11.4, 6.9 Hz), 56.60, 54.60, 16.48 (d, J = 5.7 Hz), 16.29 (d, J = 5.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 21.65 ppm. HRMS (ESI) m/z calcd for $C_{29}H_{30}N_3O_3P$ [M + Na^+]: 522.1911; Found 522. 1916.

4.2.14 | Diethyl [3-phenoxy(p-phenylazoaniline)methyl] phosphonate (4o)

Yield: 94%, as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85-7.71 (m, 4H, ArH), 7.51-7.35 (m, 3H, ArH), 7.34-7.19 (m, 4H, ArH), 7.15-7.00 (m, 2H, ArH), 6.98-6.90 (m, 3H, ArH), 6.66 (d, J = 7.0 Hz, 2H, ArH), 5.30-5.21 (m, 1H, NH), 4.82 (dd, J = 24.2, 7.8 Hz, 1H, HCP), 4.23-4.06 (m, 2H, –OCH_2–CH_3), 4.02-3.95 (m, 1H, –OCH_2–CH_3), 3.85-3.70 (m, 1H, –OCH_2–CH_3), 1.30 (t, J = 7.0 Hz, 3H, –OCH_2–CH_3), 1.17 (t, J = 7.0 Hz, 3H, –OCH_2–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.59, 156.87, 152.98, 148.86 (d, J = 18.2 Hz), 145.57, 137.50, 130.09, 129.80, 128.98, 124.93, 123.43, 123.28, 122.61 (d, J = 5.3 Hz), 122.35, 118.87, 118.44, 118.22 (d, J = 9.6 Hz), 113.64, 63.52 (dd, J = 12.4, 7.0 Hz), 56.62, 54.62, 16.47 (d, J^3_{CP} = 5.9 Hz), 16.28 (d, J^3_{CP} = 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 21.93 ppm. HRMS (ESI) m/z calcd for $C_{29}H_{30}N_3O_4P$ [M + H^+]: 516. 2027; Found 516.2046.

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