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A novel straightforward synthesis of α-aminophosphonates: one-pot three-component condensation of alcohols, amines, and diethylphosphite in the presence of $CuO@Fe_3O_4$ nanoparticles as a catalyst

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Abstract We report here a novel and straightforward synthesis method for the preparation of α-aminophosphonates in relatively good yield. The method involves the one-pot three-component condensation of alcohols, amines, and diethylphosphite in the presence of $CuO@Fe_3O_4$ nanoparticles as a recyclable catalyst. $CuO@Fe_3O_4$ nanoparticles were prepared and their structures were confirmed by the FT-IR, TGA, VSM, TEM and X-ray diffraction patterns analyses.

Keywords $CuO@Fe_3O_4$ Nanoparticles · Alcohols · Amines · α-Aminophosphonates · Oxidation · Nanocatalyst

Introduction

Organophosphorus compounds are an important class of compounds that they have a variety of interesting and useful properties in biological activities [1–8]. Recently, the synthesis of α-substituted phosphonic derivatives has attracted significant attention, due to their biological activities with broad application as enzyme inhibitors, antimetabolites and antibiotics [9–11]. Among α-functionalized phosphonic acids, α-aminophosphonates, as phosphorus analogues of α-amino acids, exhibit a variety of biological activities [12–17]. The Kabachnik–Fields [18–20] method is a three-component condensation reaction of primary or secondary amines,

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carbonyl compounds and dialkyl phosphites, and represents a convenient choice for the synthesis of α-aminophosphonates. In general, these three-component reactions may take place via hydrophosphorylation of a Schiff's base imine catalyzed by a base or an acid [21–23].

Magnetic nanoparticle-supported catalysts have attracted much attention in developing greener and efficient catalytic reactions in organic transformations [24–31]. These nanoparticles with highly active surface areas and readily dispersible in the reaction system are very accessible to the reactants and can be simply removed and readily reused from the reaction medium by an external magnet.

Different catalytic systems have been employed for the oxidation of alcohols to carbonyl compounds [32–34]. Copper derivatives, especially copper halides and oxides, are often employed for the oxidation process [35]. Due to loss of homogenous copper catalysts at end of the reaction, different strategies have been followed using supported copper catalysts on inorganic materials or immobilization on organic–inorganic hybrid materials [36]. Recently, supported copper oxide on magnetite has been reported as a nanocomposite in organic transformations [37]. Ramon et al. have reported synthesis of aromatic imines from alcohols and amines using an impregnated copper on magnetite catalyst [38]. This report suggested to us that the imines generated through the oxidation and condensation process of alcohols with amines would react with diethyl phosphite in the presence of $CuO@Fe_3O_4$ as a catalyst. To the best of our knowledge, there is no report on the synthesis of α-aminophosphonates via a one-pot condensation of alcohols, amines and diethyl phosphate. Therefore, as a part of our efforts to explore the utility of magnetite nanoparticles for the synthesis of organophosphorus compounds [39, 40], we decided to study the feasibility of the $CuO@Fe_3O_4$ nanocomposite as a catalyst in a one-pot reaction of alcohols with amines and dialkyl phosphites for the synthesis of α-aminophosphonates.

Results and discussion

The magnetic nanoparticles were prepared by simple co-precipitation of a mixture of iron precursors (Fe^{2+} and Fe^{3+}) in the presence of an ammonia solution [41]. The superparamagnetic $CuO@Fe_3O_4$ nanoparticles were prepared by hydrolysis and condensation of copper (II) chloride in water at ambient temperature in the presence of sodium hydroxide (Fig. 1) [38]. The morphology and structure of the prepared $CuO@Fe_3O_4$ nanoparticles were characterized by TEM, XRD, and VSM which

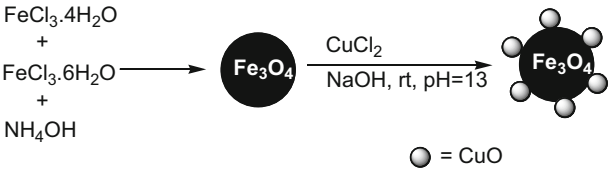


Fig. 1 $CuO@Fe_3O_4$ nanoparticles preparation

confirmed the successful preparation of nanoparticles (see supporting information). Incorporation of 4.82% (the weight percent) of Cu was measured by atomic absorption spectrometry (Fig. 1). The nanoparticles sizes of $CuO@Fe_3O_4$ were determined from the XRD pattern using Scherrer's equation (the nanoparticle sizes evaluated by Scherrer's equation are 20 nm).

Initially, the reaction of benzyl alcohol **1a** with aniline **2a** was chosen as a model for the in situ oxidative imine formation in the presence of $CuO@Fe_3O_4$ nanoparticles (Scheme 1). Treatment of **1a** with aniline (1 equiv) at room temperature in the absence of base in toluene failed to give the corresponding imine **3a** for 4 days (Entry 1). Ramon et al. have reported that using a base is necessary in oxidative imine formation of alcohols [38]. However; the reaction did not change upon adding the base (NaOH, 1.5 equiv) at room temperature for 4 days. Heating of benzyl alcohol (**1a**) with aniline (**2a**) at 100 °C in the presence of NaOH (1.5 equiv) with toluene for 24 h led to the formation of the desired imine **3a** in 56% yield (Table 1, Entry 3). The yield of the reaction was increased upon further increase of the reaction time (Entries 4–6). The reaction yield was increased to 85% yield after 4 days in the presence of 1.5 mol % of $CuO@Fe_3O_4$ (Entry 6). When the catalyst loading was raised from 1.5 to 2.5%, the yield of **3a** slightly increased to 86% (Entry 7). The yield of the reaction did not change upon further increase of the catalyst or reaction time (Entries 8 and 9). When the reaction was carried out in CH_3CN and dioxane as a solvent, the reaction yield decreased to 14 and 33% yield, respectively (Entries 10 and 11). Treatment of **1a** with **2a** at 100 °C in the presence of Fe_3O_4 nanoparticles (1.5 mol %) gave the corresponding imine **3a** in 8% yield (Entries 12). Thus, the optimal reaction conditions for the oxidative imine formation in the presence of $CuO@Fe_3O_4$ nanoparticles involved the use of 1.5 mol % of the catalyst at 100 °C for 4 days.

In the next step, treatment of diethyl phosphite with a mixture of benzyl alcohol **1a** and aniline **2a** in the presence of $CuO@Fe_3O_4$ nanoparticles gave the corresponding α-aminophosphonate **4a** in 70% yield after 24 h (Scheme 2).

This process was successfully applied to other alcohol and aniline derivatives as summarized in Table 2 (Scheme 3). Substituted benzyl alcohols reacted with a mixture of aniline and diethylphosphite in the presence of 1.5 mol % of $CuO@Fe_3O_4$ and NaOH (1.5 equiv) as the base to afford the desired products **4b–4e** in moderate to good yields. However, treatment of *p*-nitrobenzyl alcohol with aniline in the presence of diethyl phosphite under the same condition, failed to give the expected α-aminophopsphonate (Entry 6) and that maybe is due to more reactivity of the alcohol substrate to oxidize to corresponding carboxylic acid. Substituted anilines also reacted with benzyl alcohol and diethyl phosphite under optimized reaction conditions and gave the desired products **4f–4j** in moderate to

Scheme 1 Reaction of benzyl alcohol (1 equiv) with aniline (1 equiv) in the presence of $CuO@Fe_3O_4$ as a catalyst

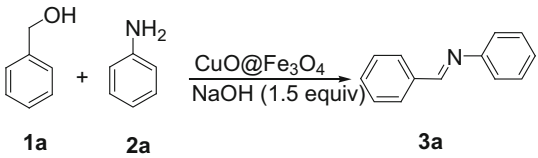


Table 1 Reaction of benzyl alcohol (1 equiv) with aniline (1 equiv)

Entry	Mol % of catalyst	Temperature (°C)	Time (d)[a]	Yield %[b] **3a**
1	1.5	Rt	4	–[c]
2	1.5	Rt	4	–
3	1.5	100	1	56
4	1.5	100	2	73
5	1.5	100	3	83
6	1.5	100	4	85
7	2.5	100	4	86
8	3.5	100	4	86
9	3.5	100	6	86
10	1.5	Reflux	4	14[d]
11	1.5	100	4	33[e]
12	1.5	100	4	8[f]

[a] Reactions carried out in toluene

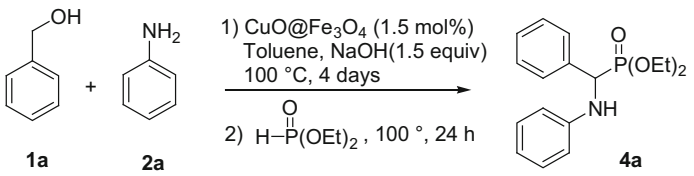
[b] GC yield

[c] Without any base

[d] Acetonitrile as solvent

[e] Dioxane as solvent

[f] The reaction carried out in the presence of Fe_3O_4 nanoparticles



Scheme 2 Treatment of diethyl phosphite with a mixture of benzyl alcohol (1 equiv) and aniline (1 equiv) in the presence of $CuO@Fe_3O_4$ as a catalyst

good yields (Entries 8–12). The process was also successfully applied for 1-naphthalenemethanol, and the compound **4j** was obtained in 57% isolated yield (Entry 12). Treatment of 1-butanol and furan-2-ylmethanol with aniline, and also benzyl alcohol with butyl amine in the presence of diethyl phosphite under the same condition, failed to give the expected α-aminophopsphonate (Entries 13–15).

The reusability of the $CuO@Fe_3O_4$ catalyst was also studied for the reaction of benzyl alcohol **1a** with aniline **2a** and diethylphosphite in the presence of NaOH. The nanoparticles were collected by an external magnet, and the particles was washed four times with deionized water and methanol and reused after drying at 90 °C for 3 h for the synthesis of α-aminophosphonates. The catalytic activity did not decrease considerably after four catalytic cycles (2% decreases after four catalytic cycles).

Table 2 Reaction of alcohols **1** with amines **2** in the presence of diethylphosphite using $CuO@Fe_3O_4$ nanocatalyst

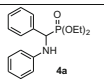
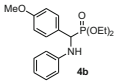
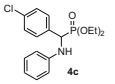
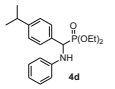
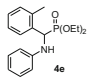
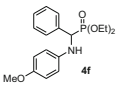
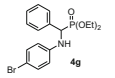
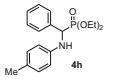
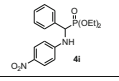
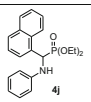
Entry	Alcohol **1**	Amine **2**	Product **4**	Reaction time (h)[a]	Yield (%)[b]	^{31}P NMR δ (ppm) **4**
1	 **1a**	 **2a**	 **4a**	24	70	22.59
2	 **1b**	 **2a**	 **4b**	48	67	22.89
3	 **1c**	 **2a**	 **4c**	24	65	21.96
4	 **1d**	 **2a**	 **4d**	36	62	22.89
5	 **1e**	 **2a**	 **4e**	48	66	22.59
6	 **1f**	 **2a**	–[c]	48	–	–
7	 **1g**	 **2a**	–[c]	48	–	–
8	 **1a**	 **2b**	 **4f**	48	63	22.69
9	 **1a**	 **2c**	 **4g**	24	69	22.19
10	 **1a**	 **2d**	 **4h**	24	70	22.73
11	 **1a**	 **2e**	 **4i**	24	72	21.26

Table 2 continued

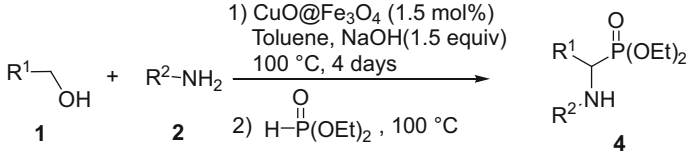
Entry	Alcohol **1**	Amine **2**	Product **4**	Reaction time (h)[a]	Yield (%)[b]	^{31}P NMR δ (ppm) **4**
12				24	57	22.94
13			–[d]	48	–	–
14			–[c]	48	–	–
15			–[d]	48	–	–

[a] Reaction time is for second step

[b] Yields refer to the isolated pure products after column chromatography

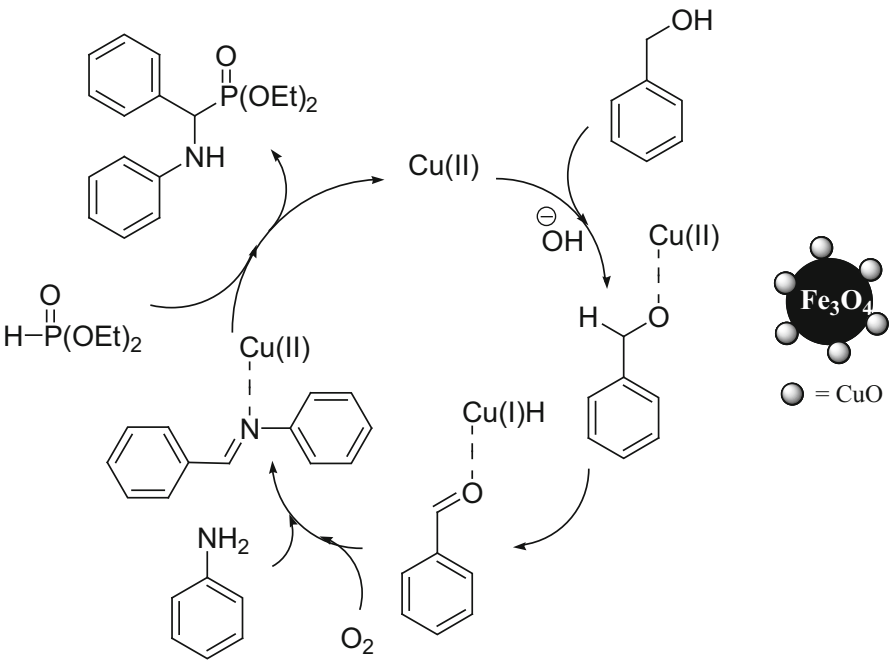
[c] Unknown mixture

[d] No reaction



Scheme 3 Treatment of diethyl phosphite with a mixture of alcohol (1 equiv) and amine (1 equiv) in the presence of $CuO@Fe_3O_4$ as a catalyst

A proposed mechanism is outlined in Scheme 4 for the synthesis of α-aminophosphonates from the reaction of alcohols with amines in the presence of diethyl phosphite using $CuO@Fe_3O_4$ nanoparticles. The present process is thought to proceed via oxidative imine formation from alcohols and amines using $CuO@Fe_3O_4$ nanoparticles, a known intermediate, followed by nucleophilic addition of diethyl phosphite with the imine intermediate to give the α-aminophosphonates **4**. As shown in Scheme 4, a simple mechanism for CuO catalyzed benzaldehyde formation from benzyl alcohol is in agreement with reports by Riisager et al. [42]. The alcohol adsorbs on a copper site of the catalyst to form a metal–alkoxide intermediate followed by abstraction of proton from the OH group by oxygen on the surface of the catalyst. Subsequently, a β-H elimination process occurs by Cu(II) to give Cu(I) hydride and a benzyl carbocation intermediate followed by aldehyde formation. In the final step, atmospheric oxygen reacts with



Scheme 4 Proposed mechanism for the synthesis of α-aminophosphonate **4**

the hydride forming the peroxide anion and regenerating the catalytic Cu(II) site. Reaction of the peroxide anion with a second hydride reduces it further to hydroxide anions [43, 44]. The reaction was carried out in an open flask, and we found no difference in yield between the reactions carried out with or without air.

In conclusion, we have reported a novel and convenient method for the synthesis of α-aminophosphonates via a one-pot condensation of alcohols, amines and diethyl phosphite. A simple work-up, mild reaction conditions, moderate to good yields, reusability of the catalyst, and clean reactions should make this method an attractive and a useful contribution to present methodologies.

Experimental

General

All solvents and reagents were purchased from commercial sources and used without further purification. All melting points were taken on a Yanagimoto and Buchi 510 apparatus and are not corrected. NMR spectra were obtained on a Bruker Avance 400 NMR spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz, ^{31}P NMR: 162.0 MHz). Analytical TLC was carried out with Merck plates precoated with silica gel 60 F254 (0.25 mm thick).

Procedure for the preparation of CuO@Fe_3O_4 nanoparticles catalyst

This catalyst was obtained according to the method reported in the literature [38]. $FeCl_3{\cdot}6H_2O$ (4.72 g) and $FeCl_2{\cdot}4H_2O$ (1.72 g) were dissolved in 40 mL distilled water under stirring at 90 °C and argon gas. Then, 20 mL of ammonia (25%) was added drop-wise to the reaction mixture with stirring. Prepared nanoparticles were magnetically separated and washed with deionized water repeatedly and dried in vacuum. Prepared Fe_3O_4 nanoparticles (4 g, 17 mmol) were added to a stirred solution of $CuCl_2$ (0.13 g, 1 mmol) in deionised water (120 mL). After 10 min at room temperature, the mixture was slowly basified with NaOH 1 M until the pH was around 13, and the mixture was stirred for 24 h and then filtrated under vacuum. The solid catalyst was washed several times with deionised water (3 × 50 mL) and dried for 3 days at room temperature.

General procedure for the synthesis of α-aminophosphonates (4) from the one-pot three-component condensation of alcohols, amines, and diethylphosphite

To a mixture of CuO@Fe_3O_4 nanoparticles (40 mg, 1.3 mol % based on copper) and NaOH (1.4 mmol, 56 mg) in toluene (3 mL), alcohol (1 mmol) and amine (2 mmol) were added, and the mixture was stirred at 100 °C for 4 days in an open flask. Diethylphosphite (1 mmol, 0.13 ml) was added to the reaction mixture, and the mixture was stirred for 24–48 h (see Table 2) at 100 °C. The reaction progress was monitored by TLC until the completion of the reaction. After cooling, EtOAc (5 mL) was added to the reaction mixture, and the catalyst was separated by an external magnet, washed thoroughly with methanol and distilled water and dried at 90 °C for 3 h for the next reaction. Then, the product was extracted by EtOAc (3 × 10 mL). The combined organic phases were concentrated. The residue was purified with column chromatography to give α-aminophosphonate **4** in 57–72% isolated yield. All α-aminophosphonate **4** gave satisfactory spectral data in accord with the assigned structures and literature reports.

O,O′-Diethyl [(*anilino*)*phenylmethyl*] *phosphonate* (***4a***) White solid (70%, 220 mg); mp: 91–93 °C [Lit [45]. 90–92 °C];^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.15 (t, 3H, $J = 7.2$ Hz), 1.32 (t, 3H, $J = 7.2$ Hz), 3.67–3.74 (m, 1H), 3.94–4.00 (m,1H), 4.12–4.19 (m, 2H), 4.81 (d, 2H, br, NH + CHP $J_{PH} = 24.0$ Hz), 6.65(d, 2H, $J = 8.0$ Hz), 6.73 (t, 1H, $J = 7.6$ Hz), 7.14 (t, 2H, $J = 7.6$ Hz), 7.28–7.31 (m, 1H), 7.36 (t, 2H, $J = 7.6$ Hz), 7.52 (d, 2H, $J = 7.2$ Hz)^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.2 (d, $J_{PC} = 6.0$ Hz), 16.4 (d, $J_{PC} = 6.0$ Hz), 55.6 (d, $J_{PC} = 150.0$ Hz), 63.2 (d, $J_{PC} = 7.0$ Hz) 63.3 (d, $J_{PC} = 7.0$ Hz), 114.0, 118.5, 127.9, 127.9 (d, $J_{PC} = 4.0$ Hz), 128.6 (d, $J_{PC} = 3.0$ Hz), 129.20, 135.82 (d, $J_{PC} = 3.0$ Hz), 146.19 (d, $J_{PC} = 15.0$ Hz) ^{31}P NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 22.59.

O,O′-Diethyl [(*anilino*)(*4-methoxyphenyl*)*methyl*] *phosphonate* (***4b***) White solid (67%, 235 mg); mp: 105–107 °C [Lit [46]. 104-106 °C];^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.17 (t, 3H, $J = 7.2$ Hz), 1.31 (t, 3H, $J = 7.2$ Hz), 3.69–3.76 (m,

1H), 3.80 (s, 3H), 3.95–4.02 (m, 1H), 4.11–4.18 (m, 2H), 4.75 (d, 1H, J_{HP} = 24.0 Hz), 6.63 (d, 2H, J = 7.2 Hz), 6.72 (t, 1H, J = 7.6 Hz), 6.89 (d, 2H, J = 8.4 Hz), 7.13 (t, 2H, J = 8.0 Hz), 7.42 (dd, 2H, J = 8.8 and 2.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 16.3 (d, J_{PC} = 6.0 Hz), 16.5 (d, J_{PC} = 6.0 Hz), 55.4 (d, J_{PC} = 150.0 Hz), 55.2, 63.2 (d, J_{PC} = 6.0 Hz), 63.3 (d, J_{PC} = 6.0 Hz), 113.9, 114.0 (d, J_{PC} = 3.0 Hz), 118.4, 127.6 (d, J_{PC} = 3.0 Hz), 129.0 (d, J_{PC} = 6.0 Hz), 129.2, 146.3 (d, J_{PC} = 15.0 Hz), 159.3 (d, J_{PC} = 3.0 Hz).^{31}P-NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 22.89.

O,O′-Diethyl [(*anilino*)(*4-chlorophenyl*)*methyl*] *phosphonate* (***4c***) White solid (65%, 230 mg); mp: 75–77 °C [Lit [47]. 73–75 °C];^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.19 (t, 3H, J = 7.2 Hz), 1.32 (t, 3H, J = 7.2 Hz), 3.78–3.84 (m, 1H), 3.99–4.05 (m,1H), 4.09–4.21 (m, 2H), 4.78 (d, 1H, J_{PH} = 24.0 Hz), 6.60 (d, 2H, J = 8.0 Hz), 6.75 (t, 1H, J = 7.2 Hz), 7.14 (t, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.45 (dd, 2H, J = 7.4 and 2.4 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.3 (d, J_{PC} = 5.0 Hz), 16.4 (d, J_{PC} = 6.0 Hz), 55.80 (d, J_{PC} = 150.0 Hz), 63.43 (d, J_{PC} = 7.0 Hz) 63.50 (d, J_{PC} = 7.0 Hz), 114.25, 119.07 128.85 (d, J_{PC} = 3.0 Hz), 129.23, 129.27, 133.82 (d, J_{PC} = 4.0 Hz), 134.32 (d, J_{PC} = 3.0 -Hz), 145.75 (d, J_{PC} = 15.0 Hz).^{31}P NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 21.96.

O,O′-Diethyl [(*anilino*)(*4-isopropylphenyl*) *methyl*] *phosphonate* (***4d***) White solid (62%, 225 mg); mp: 126–128 °C [Lit [48]. 124 °C]; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.12 (t, 3H, J = 7.2 Hz), 1.24 (d, 6H, J = 6.8 Hz), 1.31 (t, 3H, J = 7.2 Hz), 2.90 (sep, 1H J = 6.8 Hz,), 3.68–3.73 (m, 1H), 3.93–3.99 (m, 1H), 4.11–4.17 (m, 2H), 4.77 (d, 1H, J_{PH} = 24.0 Hz), 6.65 (d, 2H, J = 7.6 Hz), 6.73 (t, 1H, J = 7.6 Hz), 7.14 (t, 2H, J = 8.0 Hz), 7.21 (d, 2H, J = 8.0 Hz), 7.41 (dd, 2H, J = 8.00 and 2.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.17 (d, J_{PC} = 6.0 Hz), 16.40 (d, J_{PC} = 5.0 Hz), 23.96, 33.78, 55.81 (d, J_{PC} = 150.0 Hz), 63.22 (d, J_{PC} = 5.0 Hz), 63.28 (d, J_{PC} = 5.0 Hz), 113.98, 118.42, 126.70 (d, J_{PC} = 3.0 Hz), 127.78 (d, J_{PC} = 6.0 Hz), 129.18, 132.95, 146.30 (d, J_{PC} = 14.0 Hz), 148.64 (d, J_{PC} = 4.0 Hz).^{31}P-NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 22.44.

O,O′-Diethyl [(*anilino*)(*2-methylphenyl*)*methyl*]*phosphonate* (***4e***) [49] White solid (66%, 220 mg); mp: 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.08 (t, 3H, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz), 2.55 (s, 3H) 3.54–3.60 (m, 1H), 3.88–3.95 (m,1H), 4.14–4.20 (m, 2H), 4.99 (d, 1H, J_{PH} = 23.6 Hz), 6.6 (d, 2H, J = 8.0 Hz), 6.72 (t, 1H, J = 7.2 Hz), 7.13 (t, 2H, J = 8.0 Hz), 7.18–7.25 (m, 3H), 7.55–7.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.14 (d, J_{PC} = 6.0 Hz), 16.46 (d, J_{PC} = 6.0 Hz), 19.80 (s, 1C), 55.85 (d, J_{PC} = 150.0 Hz), 63.16 (d, J_{PC} = 7.0 Hz) 63.41 (d, J_{PC} = 7.0 Hz), 113.87, 118.61, 126.56 (d, J_{PC} = 3.0 Hz), 127.16 (d, J_{PC} = 4.0 Hz), 127.78, (d, J_{PC} = 4.0 Hz), 129.24, 130.52 (d, J_{PC} = 3.0 Hz), 133.91 (d, J_{PC} = 3.0 Hz), 136.40 (d, J_{PC} = 7.0 Hz), 145.83 (d, J_{PC} = 15.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 23.28. Anal. Calcd for $C_{18}H_{24}NO_3P$, C, 64.83; H, 7.26; N, 4.20. Found: C, 65.05; H, 7.28; N, 4.12.

O,O′-Diethyl[(*4-methoxyphenylamino*) (*phenyl*) *methyl*] *phosphonate* (***4f***) White solid (63%, 230 mg); mp: 88–90 °C [Lit [50]. colorless oil]; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.14 (t, 3H, $J = 7.2$ Hz), 1.31 (t, 3H, $J = 7.2$ Hz), 3.68–3.74 (m, 1H), 3.72 (s, 3H), 3.93–4.99 (m,1H), 4.11–4.18 (m, 2H), 4.72 (d, 1H, $J_{PH} = 24.0$ - Hz), 6.59 (d, 2H, $J = 8.8$ Hz), 6.71 (d, 2H, $J = 8.8$ Hz), 7.27–7.31 (m, 1H), 7.33–7.37 (m, 2H); 7.49 (d, 2H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.23 (d, $J_{PC} = 5.0$ Hz), 16.47 (d, $J_{PC} = 5.0$ Hz), 55.65, 56.54 (d, $J_{PC} = 150.0$ Hz), 63.26 (d, $J_{PC} = 5.0$ Hz) 63.32 (d, $J_{PC} = 4.0$ Hz), 114.73, 115.51, 127.95, 128.00, 128.60 (d, $J_{PC} = 2.0$ Hz), 135.87, 140.09 (d, $J_{PC} = 17.0$ - Hz), 152.83; ^{31}P NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 22.69.

O,O′-Diethyl[(*4-bromophenylamino*)(*phenyl*) *methyl*] *phosphonate* (***4g***) White solid (69%, 274 mg); mp: 117–120 °C [Lit [46]. 121–123 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.11 (t, 3H, $J = 7.2$ Hz), 1.30 (t, 3H, $J = 7.2$ Hz), 3.65–3.71 (m, 1H), 3.92–3.98 (m,1H), 4.10–4.20 (m, 2H), 4.69 (d, 1H, $J_{PH} = 24.0$ Hz), 6.50 (d, 2H, $J = 8.8$ Hz), 7.20 (d, 2H, $J = 8.8$ Hz), 7.29–7.38 (m, 3H), 7.46 (d, 2H, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.19 (d, $J_{PC} = 6.0$ Hz), 16.44 (d, $J_{PC} = 6.0$ Hz), 55.40 (d, $J_{PC} = 150.0$ Hz), 63.32 (d, $J_{PC} = 7.0$ Hz) 63.50 (d, $J_{PC} = 7.0$ Hz), 110.38 (s, 1C), 115.66 (s, 1C), 127.82 (d, $J_{PC} = 6.0$ Hz), 145.1 (d, $J_{PC} = 5.0$ Hz).^{31}P NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 22.19.

O,O′-Diethyl[(*4-methylphenylamino*)(*phenyl*)*methyl*] *phosphonate* (***4h***) ;White solid (70%, 233 mg); mp: 118–120 °C [Lit [51]. 117–119 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.14 (t, 3H, $J = 6.8$ Hz), 1.31 (t, 3H, $J = 6.8$ Hz), 2.21 (s, 3H) 3.69–3.75 (m, 1H), 3.94–4.00 (m,1H), 4.11–4.18 (m, 2H), 4.77 (d, 1H, $J_{PH} = 24.0$ Hz), 6.55 (d, 2H, $J = 8.4$ Hz), 6.94 (d, 2H, $J = 8.0$ Hz), 7.27–7.30 (m, 1H), 7.36 (t, 2H, $J = 8.0$ Hz), 7.50 (d, 2H, $J = 7.6$ Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.22 (d, $J_{PC} = 5.0$ Hz), 16.47 (d, $J_{PC} = 6.0$ Hz), 20.40, 56.49 (d, $J_{PC} = 150.0$ Hz), 63.27 (d, $J_{PC} = 4.0$ Hz) 63.34 (d, $J_{PC} = 4.0$ Hz), 114.20,,127.93, 127.95, 128.59, 128.61, 129.69, 135.88, 143.77 (d, $J_{PC} = 14.0$ Hz); ^{31}P NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 22.73.

O,O′-Diethyl[(*4-nitrophenylamino*)(*phenyl*)*methyl*] *phosphonate* (***4i***) Yellow solid (72%, 210 mg); mp: 148–150 °C [Lit [52]. obtained as yellow solid]; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.12 (t, 3H, $J = 7.2$ Hz), 1.33 (t, 3H, $J = 7.2$ Hz), 3.60–3.67 (m, 1H), 3.91–3.97 (m,1H), 4.12–4.22 (m, 2H), 4.83 (d, 1H, $J_{PH} = 24.0$ Hz), 6.61 (d, 2H, $J = 9.2$ Hz), 7.32–7.41 (m, 3H), 7.41 (d, 2H, $J = 7.6$ Hz), 8.04 (d, 2H, $J = 9.2$ Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.20 (d, $J_{PC} = 5.0$ Hz), 16.75 (d, $J_{PC} = 6.0$ Hz), 55.58(d, $J_{PC} = 150.0$ Hz), 63.37 (d, $J_{PC} = 7.0$ Hz) 63.95 (d, $J_{PC} = 6.0$ Hz), 112.47, 126.14, 127.73 (d, $J_{PC} = 5.0$ Hz), 128.58 (d, $J_{PC} = 2.0$ Hz), 128.97, (d, $J_{PC} = 1.0$ Hz), 134.51 (d, $J_{PC} = 3.0$ Hz), 139.09, 151.76 (d, $J_{PC} = 14$ Hz); ^{31}P NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 21.26.

O,O′-Diethyl [(*1-naphthyl*)(*phenylamino*) *methyl*] *phosphonate* [***4j***] ;White solid (57%, 210 mg); mp: 126–127 °C [Lit [53]. 125–126 °C]. ^{1}H NMR (400 MHz,

$CDCl_3$): δ (ppm) 0.76 (t, 3H, $J = 7.2$ Hz), 1.36 (t, 3H, $J = 7.2$ Hz), 3.22–3.24 (m, 1H), 3.72–3.77 (m,1H), 4.18–4.23 (m, 2H), 5.67 (d, 1H, $J_{PH} = 24.0$ Hz), 6.57(d, 2H, $J = 7.6$ Hz), 6.68 (t, 1H, $J = 7.6$ Hz), 7.07 (t, 2H, $J = 7.6$ Hz), 7.47 (t, 1H, $J = 7.6$ Hz,), 7.57 (t, 1H, $J = 7.6$ Hz), 7.65 (t, 1H, $J = 7.6$ Hz), 7.79–8.82 (m,2H), 7.93(d, 1H, $J = 8.0$ Hz), 8.28 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.7 (d, $J_{PC} = 6.0$ Hz), 16.5 (d, $J_{PC} = 6.0$ Hz), 51.3 (d, $J_{PC} = 150.0$ Hz), 63.2 (d, $J_{PC} = 7.0$ Hz) 63.4 (d, $J_{PC} = 7.0$ Hz), 113.6, 118.3, 122.9, 125.3125.4125.6 (d, $J_{PC} = 4.0$ Hz), 126.3, 128.5(d, $J_{PC} = 4.0$ Hz), 129.0, 129.2, 131.6 (d, $J_{PC} = 3.0$ Hz), 131.7 (d, $J_{PC} = 4.0$ Hz), 133.8 (d, $J_{PC} = 2.0$ Hz), 146.1 (d, $J_{PC} = 14.0$ Hz);^{31}P NMR (162 MHz, $CDCl_3/H_3PO_4$): δ (ppm) 22.94.

Supporting information

Copies of ^{31}P NMR, ^{1}H NMR and ^{13}C NMR for compounds **4a**–**4j**. Supplementary data associated with this article can be found in the online version.

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