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Zinc Di(L-prolinate)-Mediated Synthesis of α-Aminophosphonates under Mild Conditions

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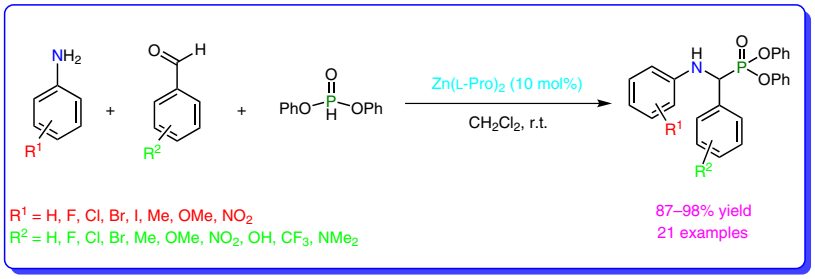

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Abstract An efficient method has been developed for the preparation of α-aminophosphonates by using zinc di(L-prolinate) as a catalyst under mild reaction conditions. The method has the advantages of high yields, short reaction times, and easy workup conditions.

Key words Kabachnik–Fields reaction, aminophosphonates, multicomponent reactions, hybrid catalysts

α-Aminophosphonates are compounds that contain an N–C–P(O) group. Such compounds have attracted increasing attention over recent years as structurally and biologically important analogues of amino acids. Moreover, α-aminophosphonates are useful as building blocks for the synthesis of antibodies,[1] and many examples show significant biological activities, such as antibacterial,[1] anti-HIV,[2] and antitumor activities.[3,4] Moreover, their analogues are also useful as pharmacological agents,[5] herbicides, fungicides, etc.[5] The most important reaction for preparing α-aminophosphonates is the Kabachnik–Fields reaction,[6] a multicomponent reaction of an amine with a trialkyl or diaryl phosphite and an aldehyde; these reactions are catalyzed by using Lewis or Brønsted acids[7–9] or by organocatalysts.[10]

However, only a few such procedures have been described in the literature, and these have several disadvantages, such as air- or chloride-sensitive catalysts, expensive catalysts, stoichiometric amounts of catalysts, potential explosiveness of catalysts, complicated workup procedures, or low yields. Besides, most of the known catalysts require prolonged reaction times and high temperature, and they are environmentally toxic.[10] In this regard, the development of a new catalyst for the Kabachnik–Fields reaction that overcomes these disadvantages is required.

We therefore studied some hybrid materials for use as new efficient catalysts in several reactions,[11–13] and we used zinc(II) di(L-prolinate) [Zn(L-Pro)$_2$] (Figure 1) as a catalyst for the Kabachnik–Fields reaction. Zn(L-Pro)$_2$ is an efficient, stable, inexpensive, nontoxic Lewis acid catalyst that is soluble in water but insoluble in most organic solvents. These properties make it potentially useful as a catalyst for the Kabachnik–Fields reaction.

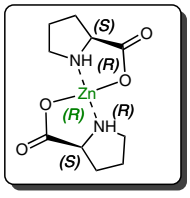

Figure 1 Structure of zinc(II) di(L-prolinate)

We prepared a series of α-aminophosphonates from benzaldehydes, anilines, and diphenyl hydrogen phosphite by a Kabachnik–Fields reaction mediated by Zn(L-Pro)$_2$ (Scheme 1)

First, a model reaction of benzaldehyde, aniline, and diphenyl hydrogen phosphite without a catalyst failed to give the desired product after three hours (Table 1, entry 1). When we conducted the same reaction with Zn(L-Pro)$_2$ (10 mol%) as a catalyst and CH_2Cl_2 as the solvent at room temperature, we obtained the desired product in 98% yield (entry 4). Next, we examined the effects of various catalyst loadings (entries 2–4), and we found that a loading of 10 mol% was optimal.

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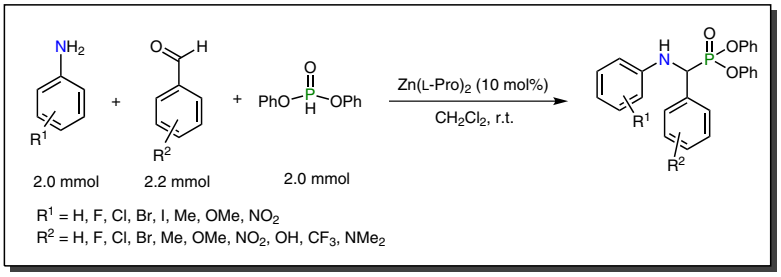


Scheme 1 Kabachnik–Fields reaction

Table 1 Effect of the Catalyst Loading on the Kabachnik–Fields Reaction

	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	0.0	180	–
2	2.5	60	30
3	5.0	40	53
4	10.0	20	98

[a] Reaction conditions: PhCHO (2.2 mmol), $PhNH_2$ (2.0 mmol), $O{=}PH(OPh)_2$ (2.0 mmol), CH_2Cl_2 (10 mL), r.t., 3 h.
[b] Isolated yield.

Next, the Zn(L-Pro)$_2$-catalyzed reaction of benzaldehyde, aniline, and diphenyl hydrogen phosphite was carried out under the standard conditions in various solvents: THF, $CHCl_3$, CH_2Cl_2, EtOH, MeOH, MeCN, and water. Among these, CH_2Cl_2 gave the best yield (Figure 2).

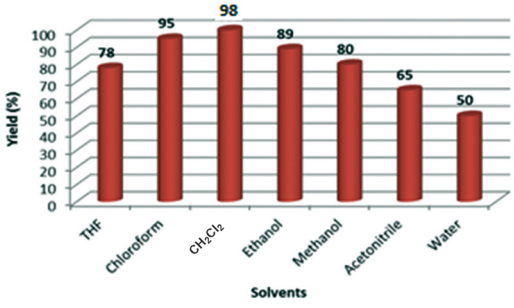
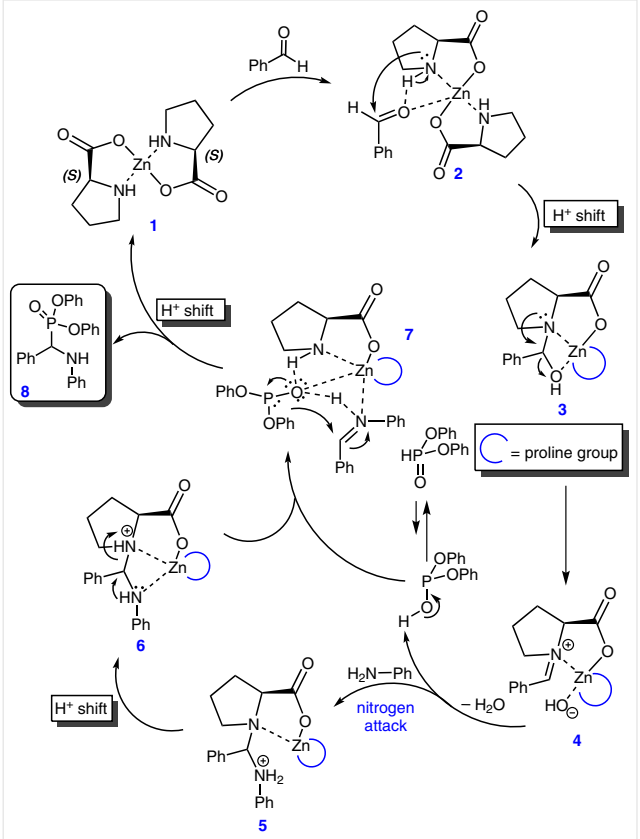


Figure 2 Effect of the solvent on the yield of the standard Kabachnik–Fields reaction

We then examined the scope of the reaction (Table 2). Benzaldehydes bearing electron-donating groups such as OMe, Me, or OH gave yields of 98, 95, and 90%, respectively (Table 2, entries 6, 7, and 11). Interestingly, benzaldehydes bearing electron-withdrawing substituents such as NO_2, Cl, F, Br, or CF_3 gave moderate to excellent yields of 89–95% (entries 2–5 and 10). Furthermore, 3-nitrobenzaldehyde, thiophene-2-carbaldehyde, and cinnamaldehyde gave yields of 87, 95 and 98%, respectively (entries 8, 12, and 13).[14] Anilines containing electron-donating or electron-withdrawing substituents also gave excellent yields of the corresponding products (entries 14–21).[15,16]

We propose the mechanistic pathway for the synthesis of α-aminophosphonates by the Zn(L-Pro)$_2$-catalyzed Kabachnik–Fields reaction that is shown in Scheme 2. First, the catalyst undergoes hydrogen bonding to benzaldehyde and the resulting complex **2** then reacts with aniline to form an imine **7**. The imine then undergoes addition to diphenyl hydrogen phosphite to give the desired α-aminophosphonate product **8**.



Scheme 2 Plausible mechanism for the synthesis of an α-aminophosphonate by the Zn(L-Pro)$_2$-mediated Kabachnik–Fields reaction

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Table 2 Scope of the Kabachnik–Fields Reaction Catalyzed by Zn(L-Pro)$_2$

Entry	Aldehyde	Amine	Time (min)	Yield[b] (%)
1	benzaldehyde	aniline	20	98
2	4-nitrobenzaldehyde	aniline	45	95
3	4-chlorobenzaldehyde	aniline	45	89
4	4-fluorobenzaldehyde	aniline	45	90
5	4-bromobenzaldehyde	aniline	45	98
6	4-methoxybenzaldehyde	aniline	60	98
7	4-methylbenzaldehyde	aniline	60	95
8	3-nitrobenzaldehyde	aniline	60	87
9	4-(dimethylamino)benzaldehyde	aniline	60	90
10	4-(trifluoromethyl)benzaldehyde	aniline	45	91
11	3-hydroxybenzaldehyde	aniline	60	90
12	thiophene-2-carbaldehyde	aniline	60	95
13	cinnamaldehyde	aniline	60	98
14	benzaldehyde	4-nitroaniline	40	96
15	benzaldehyde	4-chloroaniline	45	87
16	benzaldehyde	4-bromoaniline	60	93
17	benzaldehyde	4-fluoroaniline	60	90
18	benzaldehyde	4-iodoaniline	60	96
19	benzaldehyde	4-methoxyaniline	60	89
20	benzaldehyde	4-methylaniline	60	90
21	benzaldehyde	2,6-dimethylaniline	60	98

[a] Isolated yield after crystallization.

Note that this plausible mechanistic pathway for the synthesis of the α-aminophosphonate derivatives is similar to those given in previous reports by Siddiqui and Farooq,[17] by Reymond and co-workers[18] (intermediates **1**–**4**), and by Shibata and co-workers (intermediate **5**).[19]

Note also that our results with respect to substituent effects, times, and yields are similar to those previously reported for Kabachnik–Fields reactions with tin(II) salts as catalysts.[20]

All the products that we obtained were compared with authentic samples, and were characterized by means of ^{1}H and ^{13}C NMR and IR spectroscopy and mass spectrometric analysis.[21]

The reactions were monitored by TLC on Macherey-Nagel SIL G/ UV$_{254}$ plates visualized by fluorescence of UV irradiation at 254 nm. Products were purified by crystallization from $CHCl_3$–hexane at 65 °C. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer at 300 and 75 MHz, respectively. IR spectra were recorded on a ThermoFisher Scientific Nicolet IZ10 spectrometer with Smart OMNI-Transmission.

All spectral data matched the corresponding data in the literature.

Zinc(II) Di(L-prolinate)

$ZnCl_2$ (1 mmol) was added to a solution of L-proline (2 mmol) and NaOH (2 mmol) in EtOH (15 mL), and the mixture was stirred for 45 min at r.t. The resulting white solid was collected by filtration and dried in a desiccator for one day. The resulting hybrid catalyst was used without further purification.

Diphenyl [Anilino(phenyl)methyl]phosphonate;[21] Typical Procedure

A tube equipped with a magnetic stirrer bar was charged with Zn(L-Pro)$_2$ (0.2 mmol), PhCHO (2.2 mmol), $PhNH_2$ (2.0 mmol), and O=PH(OPh)$_2$ (2.0 mmol), and the mixture was stirred at r.t. for about 20 min until the Ph_2PH(=O) and $PhNH_2$ were completely consumed (TLC). The solvent was then removed by rotary evaporation and the resulting yellowish solid was purified by crystallization ($CHCl_3$–hexane) to give a yellow solid; yield: 812 mg (98%); mp 150–152 °C.

IR (KBr): 3343.0 (N–H), 1186.0 (P=O), 762.0 (C–P) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.57–4.60 (m, 2 H), 4.10–4.40 (m, 15 H), 3.67–3.89 (m, 4 H), 2.18 (d, J_{H-P} = 24.6 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 145.9, 134.7, 129.7, 129.5, 129.2, 128.8, 128.7, 128.2, 128.1, 128.1, 125.3, 125.2, 120.6, 120.6, 120.3, 120.2, 118.8, 76.5, 55.1, 56.9 (d, J_{C-P} = 158.6 Hz).

MS: m/z = 416 [M + 1]$^+$.

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Diphenyl [Anilino(4-nitrophenyl)methyl]phosphonate[21]

Yellow solid; yield: 875 mg (95%); mp 149–151 °C.

IR (KBr): 3305.3 (N–H), 1182.1 (P=O), 772.0 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.22 (m, 2 H), 7.67–7.81 (m, 3 H), 6.75–7.34 (m, 12 H), 6.56–6.64 (m, 3 H), 5.30 (d, *J* = 25.4 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.9, 149.8, 147.7, 145.1, 144.9, 142.7, 125.7, 125.6, 123.8, 123.7, 123.6, 120.4, 120.3, 120.1, 120.0, 119.4, 118.9, 115.3, 113.8, 113.7, 76.5, (d, J_{C-P} = 150.1 Hz) 56.7, 54.7.

MS: *m/z* = 461 $[M + 1]^+$.

Diphenyl [Anilino(4-chlorophenyl)methyl]phosphonate[21]

Brown solid; yield: 814 mg (89%); mp 131–133 °C.

IR (KBr): 3299.0 (N–H), 1182.1 (P–O), 765.6 (C–P) cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 7.51–7.57 (m, 3 H), 7.11–7.38 (m, 12 H), 6.64–6.98 (m, 5 H), 5.16 (d, *J* = 24.9 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 149.9, 145.5, 145.4, 134.2, 133.4, 129.7, 129.4, 129.3, 129.0, 128.9, 125.5, 125.3, 120.5, 120.5, 120.2, 119.1, 113.9, 76.5, 56.4 and 54.4 (d, J_{C-P} = 153.0 Hz).

MS: *m/z* = 450 $[M + 1]^+$.

Diphenyl [Anilino(4-fluorophenyl)methyl]phosphonate[21]

Yellow solid; yield: 778 mg (90%); mp 125–127 °C.

IR (KBr): 3453.2 (N–H), 1284.6 (P–O), 776.8 (C-O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.52–7.25 (m, 2 H), 7.03–7.33 (m, 12 H), 6.76–6.94 (m, 4 H), 6.63–6.66 (m, 2 H), 5.15 (d J_{H-P} = 24.0 Hz, 1 H, N–CH–P).4

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 145.7, 145.5, 129.8, 129.8, 129.7, 129.3, 125.4, 125.3, 120.6, 120.5, 120.2, 120.1, 119.0, 115.9, 115.9, 115.6, 115.6, 113.9, 76.5, 56.2 and 54.2 (d, J_{C-P} = 153.7 Hz).4

MS: *m/z* = 434 $[M + 1]^+$.

Diphenyl [Anilino(4-bromophenyl)methyl]phosphonate[21]

Brown solid; yield: 967 mg (98%); mp 140–142 °C.

IR (KBr): 3322.7 (N–H), 1029.6 (P–O), 765.6 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.42 (m, 4 H), 7.32–7.07 (m, 9 H), 6.95–6.91 (m, 2 H), 6.83–6.75 (m, 3 H), 6.63–6.61 (m, 2 H), 5.10 (d, *J* = 24.9 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6, 145.4, 134.9, 134.0, 131.9, 129.7, 129.6, 129.3, 125.5, 125.4, 122.4, 120.5, 120.4, 120.2, 120.1, 119.1, 113.9, 100.0, 76.5, 56.4 and 54.4 (d, J_{C-P} = 151.5 Hz).

MS: *m/z* = 495 $[M + 1]^+$.

Diphenyl [Anilino(4-methoxyphenyl)methyl]phosphonate[21]

Yellow solid; yield: 871 mg (98%); mp 141–143 °C.

IR (KBr): 3329.0 (N–H), 1252.0 (P–O), 770.4 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.45 (m, 2 H), 7.33–7.09 (m, 13 H), 6.93–6.65 (m, 5 H), 5.12 (d, *J* = 25.38 Hz, 1 H, N–CH–P), 3.80 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.3, 150.0, 145.9, 145.7, 129.6, 129.5, 129.3, 129.2, 129.1, 126.4, 126.3, 125.2, 125.1, 120.6, 120.5, 120.3, 120.2, 118.6, 114.2, 114.1, 113.9, 76.5, 56.2, 56.2 and 55.1, 54.1 (t, J_{C-P} = 155.2 Hz).

MS: *m/z* = 446 $[M + 1]^+$.

Diphenyl [Anilino(4-methylphenyl)methyl]phosphonate[21]

Yellow solid; yield: 814 mg (95%); mp 120–123 °C.

IR (KBr): 3345.0 (N–H), 1215.1 (P=O), 764.6 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.17–7.91 (m, 1 H), 7.60–7.45 (m, 3 H), 7.40–7.10 (m, 12 H), 7.03–6.79 (m, 5 H), 6.68–6.58 (m, 2 H), 5.16 (d, J_{H-P} = 24.6 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.2, 143.5, 143.2, 134.8, 129.7, 129.6, 129.4, 128.7, 128.2, 128.1, 125.3, 120.7, 120.6, 120.3, 120.2, 120.1, 115.6, 115.3, 114.1, 76.5, 56.2 (d, J_{C-P} = 152.2 Hz), 20.4 (s, CH_3).

MS: *m/z* = 430 $[M + 1]^+$.

Diphenyl [Anilino(3-nitrophenyl)methyl]phosphonate[21]

Yellow solid; yield: 800 mg (87%); mp 124–126 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.15–7.99 (m, 2 H), 7.61–7.11 (m, 12 H), 6.95–6.50 (m, 6 H), 5.30 (dd, *J* = 21.0, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5, 149.8, 138.9, 129.8, 129.6, 129.4, 129.0, 128.1, 128.1, 125.9, 125.8, 125.5, 120.4, 120.4, 120.2, 120.0, 115.7, 115.3, 113.2, 112.4, 55.7 and 54.4 (d, *J* C–P = 156.2 Hz).

MS: *m/z* = 461 $[M + 1]^+$.

Diphenyl {Anilino[4-(dimethylamino)phenyl]methyl}phosphonate[21]

Orange solid; yield: 756 mg (90%); mp 98–100 °C.

IR (KBr): 3399.1 (N–H), 1188.9 (P=O), 772.3 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.75 (m, 1 H), 7.43–7.39 (m, 3 H), 7.32–7.10 (m, 11 H), 6.94–6.66 (m, 5 H), 5.10 (dd, *J* = 23.6, 1 H, N–CH–P), 3.09 (s, 3 H), 2.94 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 146.1, 145.8, 129.5, 129.4, 129.0, 128.8, 128.7, 125.0, 124.9, 121.5, 120.6, 120.5, 120.3, 119.6, 118.4, 115.3, 113.9, 112.5, 110.8, 112.5, 76.4, 56.3 and 54.2 (d, J_{P-C} = 153.7 Hz), 40.3 (s, N–C).

MS: *m/z* = 459 $[M + 1]^+$.

Diphenyl {Anilino[4-(trifluoromethyl)phenyl]methyl}phosphonate[21]

Green solid; yield: 732 mg (91%); mp 118–120 °C.

IR (KBr): 3326.1 (N–H), 1209.6 (P=O), 752.1 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.44 (m, 5 H), 7.33–6.62 (m, 15 H), 5.22 (d, *J* = 25.4, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 145.4, 139.0, 129.8, 129.7, 129.5, 129.3, 128.5, 128.4, 125.6, 125.5, 120.5, 120.2, 120.1, 119.2, 115.3, 113.9, 56.3 and 55.0 (d, J_{P-C} = 153.1 Hz).

MS: *m/z* = 484 $[M + 1]^+$.

Diphenyl [Anilino(3-hydroxyphenyl)methyl]phosphonate[21]

Semi-solid; yield: 774 mg (90%).

IR (KBr): 3298.1 (N–H), 1280.0 (P=O), 770.4 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.04 (m, 6 H), 6.90–6.73 (m, 8 H), 6.47–6.34 (m, 2 H), 6.05 (s, 1 H, O-H), 4.96–4.84 (m, 3 H), 3.74 and 3.73 (dd, J_{H-P} = 15.0 Hz, J_{H-C} = 21.0, 1 H, N–CH–P), 1.25 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.40, 156.39, 146.02, 145.90, 135.99, 134.51, 134.31, 129.92, 129.82, 129.50, 128.61, 128.17, 126.76, 125.54, 123.81, 122.06, 120.78, 120.73, 120.69, 120.42, 119.95, 119.08, 115.50, 115.50, 114.04, 54.97 and 53.02 (d, J_{P-C} = 151.10 Hz).

MS: *m/z* = 432 $[M + 1]^+$.

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Diphenyl [Anilino(2-thienyl)methyl]phosphonate[21]

Brown solid; yield: 798 mg (95%); mp 133–135 °C.

IR (KBr): 3365.1 (N–H), 1277.1 (P=O), 773.3 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.58–7.37 (m, 2 H), 7.29–6.98 (m, 11 H), 6.90–6.60 (m, 6 H), 5.44 (d, *J* = 24.4, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.2, 150.1, 150.0, 145.6, 138.1, 129.7, 129.5, 129.4, 129.3, 127.2, 126.9, 125.9, 125.3, 120.9, 120.6, 120.5, 120.3, 120.2, 119.4, 115.3, 114.1, 76.7, 52.5 and 51.2 (d, *J*P-C = 162.7 Hz).

MS: *m/z* = 422 $[M + 1]^+$.

(*E*)-Diphenyl [3-Phenyl-1-(phenylamino)allyl]phosphonate[21]

Brown solid; yield: 863 mg (98%); mp 85–87 °C.

IR (KBr): 3295.7 (N–H), 1213.0 (P=O), 741.9 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.34–8.14 (m, 5 H), 7.37–7.08 (m, 10 H), 6.89–6.80 (m, 7 H), 5.67 (s, 1 H, N–H), 5.19 (d, J_{H-P} = 14.1 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 148.4, 146.0, 137.5, 137.2, 135.5, 133.8, 133.2, 132.1, 129.6, 129.4, 126.9, 121.2, 120.7, 119.9, 119.1, 117.7, 117.3, 115.3, 113.2.

MS: *m/z* = 442 $[M + 1]^+$.

Diphenyl {[(4-Nitrophenyl)amino](phenyl)methyl}phosphonate[21]

Yellow solid; yield: 883 mg (96%); mp 145–147 °C.

IR (KBr): 3328.7 (N–H), 1257.9 (P–O), 770.4 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.34–8.20 (m, 2 H), 8.05–7.96 (m, 2 H), 7.77–7.75 (m, 2 H), 7.44–6.62 (m, 14 H), 5.93 (dd, J_{H-P} = 24.6 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 153.1, 149.9, 149.8, 149.6, 137.3, 134.4, 129.7, 126.3, 125.7, 125.3, 125.2, 120.4, 120.2, 115.2, 112.3, 54.8, 52.8, 40.2, 39.9, 39.7, 39.1, 38.8 and 38.5 (d, J_{C-P} = 155.7 Hz).

MS: *m/z* = 461 $[M + 1]^+$.

Diphenyl {[(4-Chlorophenyl)amino](phenyl)methyl}phosphonate[21]

White solid; yield: 796 mg (87%); mp 150–152 °C.

IR (KBr): 3336.2 (N–H), 1185.5 (P=O), 775.7 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.33–6.28 (m, 2 H), 6.17–5.84 (m, 14 H), 5.64–5.60 (m, 2 H), 5.37–5.32 (m, 2 H), 3.86 (d, J_{H-P} = 24.6 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 144.5, 144.2, 134.3, 129.7, 129.6, 129.1, 128.9, 128.8, 128.5, 128.1, 128.0, 125.5, 125.2, 123.5, 120.6, 120.5, 120.2, 115.1, 76.5, 57.1 and 55.0 (d, J_{C-P} = 160.5 Hz).

MS: *m/z* = 450 $[M + 1]^+$.

Diphenyl {[(4-Bromophenyl)amino](phenyl)methyl}phosphonate[21]

White solid; yield: 917 mg (93%); mp 167–169 °C.

IR (KBr): 3336.2 (N–H), 1185.5 (P=O), 775.7 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.55 (m, 2 H), 7.45–7.13 (m, 14 H), 6.91–6.86 (m, 2 H), 6.60–6.55 (m, 2 H), 5.14 (d, J_{H-P} = 24.6 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.2, 144.9, 144.7, 132.0, 129.7, 129.6, 128.8, 128.5, 128.4, 128.1, 128.0, 125.4, 125.2, 120.5, 120.5, 120.2, 120.1, 115.5, 110.6, 76.5, 57.0 and 54.8 (d, J_{C-P} = 159 Hz).

MS: *m/z* = 495 $[M + 1]^+$.

Diphenyl {[(4-Fluorophenyl)amino](phenyl)methyl}phosphonate[21]

Yellow solid; yield: 777 mg (90%); mp 130–132 °C.

IR (KBr): 3343.1 (N–H), 1187.9 (P=O), 775.7 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.51 (m, 2 H), 7.33–6.90 (m, 13 H), 6.80–6.62 (m, 5 H), 5.14 (d, J_{H-P} = 24.0 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 142.1, 141.9, 134.3, 129.7, 129.6, 129.4, 128.8, 128.8, 128.5, 128.1, 128.110, 120.6, 120.5, 120.2, 120.0, 115.8, 115.5, 115.3, 115.1, 115.0, 76.5, 57.5 and 55.5 (d, J_{C-P} = 154.05 Hz).

MS: *m/z* = 434 $[M + 1]^+$.

Diphenyl {[(4-Iodophenyl)amino](phenyl)methyl}phosphonate[21]

Yellow solid; yield: 1.03 g (96%); mp 155–157 °C.

IR (KBr): 3339.6 (N–H), 1188.9 (P=O), 775.7 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.50 (m, 2 H), 7.41–7.07 (m, 14 H), 6.85–6.81 (m, 2 H), 6.45–6.40 (m, 2 H), 5.08 (d, J_{H-P} = 24.9 Hz, 1 H, N–CH–P).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.5, 145.3, 137.8, 134.2, 134.2, 129.7, 129.6, 128.9, 128.8, 128.5, 128.4, 128.1, 128.0, 125.5, 125.2, 120.6, 120.5, 120.2, 120.1, 116.1, 76.5, 56.8 and 54.6 (d, J_{C-P} = 160.5 Hz).

MS: *m/z* = 542 $[M + 1]^+$.

Diphenyl {[(4-Methoxyphenyl)amino](phenyl)methyl}phosphonate[21]

Brown solid; yield: 791 mg (89%); mp 150–152 °C.

IR (KBr): 3454.8 (N–H), 1186.0 (P=O), 776.2 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 3 H), 7.40–7.10 (m, 11 H), 6.89–6.61 (m, 6 H), 5.08 (d, J_{H-P} = 24.0 Hz, 1 H, N–CH–P), 3.73 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9, 150.5, 150.4, 150.3, 150.2, 141.0, 140.8, 136.0, 129.9, 129.0, 128.9, 128.4, 128.4, 128.0, 128.1, 125.4, 125.3, 120.9, 120.8, 120.5, 120.4, 115.3, 114.5, 56.5,and 55.4–54.4 (t, J_{C-P} = 155.2 Hz), 39.4 (s, CH_3).

MS: *m/z* = 446 $[M + 1]^+$.

Diphenyl {[(4-Methylphenyl)amino](phenyl)methyl}phosphonate[21]

White solid; yield: 772 mg (90%); mp 165–167 °C.

IR (KBr): 3336.2 (N–H), 1185.5 (P=O), 775.7 (C–P) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 1 H), 7.43–6.79 (m, 19 H), 5.81 (d, J_{H-P} = 24.6 Hz, 1 H, N–CH–P), 3.06 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 149.9, 133.1, 133.0, 129.6, 129.5, 129.2, 129.1, 129.0, 128.6, 128.3, 125.2, 125.1, 125.0, 120.6, 120.5, 120.4, 119.6, 118.6, 115.3, 114.3, 76.5, 63.4 and 61.2 (d, J_{C-P} = 161.2 Hz), 34.8 (s, CH_3).

MS: *m/z* = 430 $[M + 1]^+$.

Diphenyl {[(2,6-Dimethylphenyl)amino](phenyl)methyl}phosphonate[21]

Semi-solid; yield: 870 mg (98%).

IR (KBr): 3343.4 (N–H), 1213.0 (P=O), 755.4 (C–P) cm^{-1}.

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^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.51 (m, 3 H), 7.38–6.96 (m, 13 H), 6.86–6.72 (m, 3 H), 4.88 (d, J_{H-P} = 24.0 Hz, 1 H, N–CH–P), 2.36 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 149.9, 143.4, 135.4, 129.6, 129.4, 129.0, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 125.3, 125.1, 123.8, 122.7, 122.2, 120.5, 120.4, 120.2, 120.1, 119.8, 119.1, 59.9 and 57.9 (d, J_{C-P} = 148.5 Hz), 18.7 (s, CH_3).

MS: *m/z* = 444 $[M + 1]^+$.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588065.

References

(1) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29.
(2) Peyman, A.; Stahl, W.; Wagner, K.; Ruppert, D.; Budt, K.-H. *Bioorg. Med. Chem. Lett.* **1995**, *4*, 2601.
(3) Lavielle, G.; Hautefaye, P.; Schaeffer, C.; Boutin, J. A.; Cudennec, C. A.; Pierre, A. *J. Med. Chem.* **1991**, *34*, 1998.
(4) Hou, J.-T.; Gao, J.-W.; Zhang, Z.-H. *Appl. Organomet. Chem.* **2011**, *25*, 47.
(5) Rezaei, Z.; Khabnadideh, S.; Zomorodian, K.; Pakshir, K.; Nadali, S.; Mohtashami, N.; Mirzaei, E. F. *Int. J. Med. Chem.* **2011**, *11*, 678101; DOI 10.1155/2011/678101.
(6) Shashikumar, N. D. *J. Chem.* **2013**, *8*, 240381; DOI 10.1155/2013/240381.
(7) Wang, H.; Deng, T.; Cai, C. *J. Fluorine Chem.* **2014**, *168*, 144.
(8) Li, N.; Wang, X.; Qiu, R.; Xu, X.; Chen, J.; Zhang, X.; Chen, S.; Yin, S. *Catal. Commun.* **2014**, *43*, 184.
(9) Azizi, K.; Karimi, M.; Heydari, A. *Tetrahedron Lett.* **2014**, *55*, 7236.
(10) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 5079.
(11) Darbem, M. P.; Oliveira, A. R.; Winck, C. R.; Rinaldi, A. W.; Domingues, N. L. C. *Tetrahedron Lett.* **2014**, *55*, 5179.
(12) Winck, C. R.; Darbem, M. P.; Gomes, R. S.; Rinaldi, A. W.; Domingues, N. L. C. *Tetrahedron Lett.* **2014**, *55*, 4123.
(13) Rocha, M. P. D.; Oliveira, A. R.; Albuquerque, T. B.; da Silva, C. D. G.; Katla, R.; Domingues, N. L. C. *RSC Adv.* **2016**, *6*, 4979.
(14) Cherkasov, R. A.; Galkin, V. I. *Russ. Chem. Rev.* **1998**, *67*, 857.
(15) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1996**, *60*, 6656.
(16) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2008**, *73*, 6029.
(17) Siddiqui, Z. N.; Farooq, F. *Catal. Sci. Technol.* **2011**, *1*, 810.
(18) Kofoed, J.; Darbre, T.; Reymond, J.-L. *Chem. Commun.* **2006**, 1482.
(19) Ohara, M.; Nakamura, S.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 3285.
(20) Gallardo-Macias, R.; Nakayama, K. *Synthesis* **2010**, 57.
(21) da Silva, C. D. G.; Oliveira, A. R.; Rocha, M. P. D.; Katla, R.; Botero, E. R.; da Silva, É. C.; Domingues, N. L. C. *RSC Adv.* **2016**, *6*, 27213.

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