Synthesis B. Kaboudin et al. Paper

Trichloroisocyanuric Acid as an Efficient Reagent for the Synthesis of Phosphoroamidates via Atherton–Todd Reaction under Base-Free Conditions

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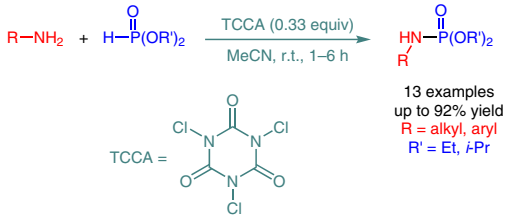

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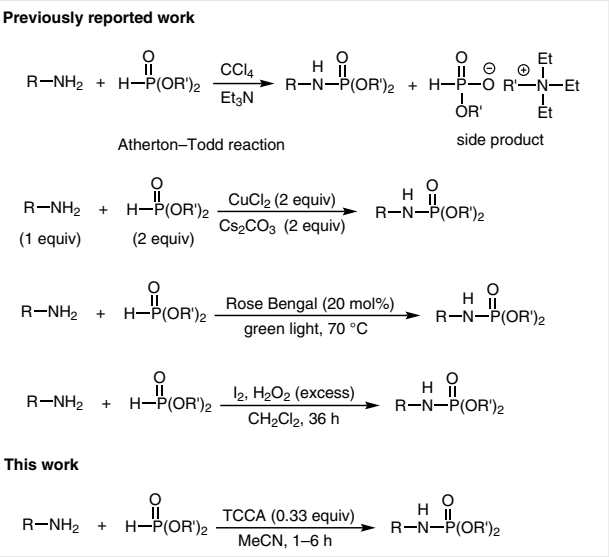
Abstract A simple, efficient, and novel method is developed for the synthesis of phosphoroamidates via an Atherton–Todd coupling reaction of amines with dialkyl H-phosphite using trichloroisocyanuric acid as an efficient and safe reagent. Treatment of amines with dialkyl H-phosphite and trichloroisocyanuric acid under base-free conditions gives phosphoroamidates in moderate to good yields. The reaction proceeded effectively to afford the corresponding phosphoroamidates via a dehydrogenative coupling of H-phosphonates with amines. This method is easy, rapid, and good-yielding for the synthesis of phosphoroamidates.

Key words phosphoroamidate, amines, dialkyl H-phosphite, coupling, Atherton–Todd reaction

Phosphorus–nitrogen bond formation is an active and important research area for the preparation of valuable intermediates in organic synthesis.[1] Among the various organophosphorus compounds including P–N bonds, phosphoroamidates are of interest as effective in biologically active molecules, medicinal chemistry, and industrially important products.[2] A number of phosphoramidates have become important chiral ligands for metal-catalyzed reactions in organic transformations.[3] A number of biologically active natural products such as agrocin 84, thymectacin (NB1011), stampidine, phosmidosine, and microcin C7 contain phosphoramidate functional groups as a key structural unit.[4] Phosphoroamidates can be also used as a prodrug for the preparation of 2′-*C*-methylcytidine, which is the first nucleoside inhibitor of HCV NS5B polymerase with their reducing activity on the viral load in patients infected with HCV.[5]

A more straightforward and common one-pot process for the synthesis of phosphoroamidates is the Atherton–Todd reaction.[6] The process involves the in situ formation of dialkyl chlorophosphate via the reaction of dialkyl phosphite with carbon tetrachloride in the presence of a base followed by a nucleophilic addition of an amine to the resulting dialkyl chlorophosphate. Other methods include the coupling reaction of dialkyl phosphite with amines in the presence of a transition metal copper salts with a base,[7] or the use of I_2 as catalyst with stoichiometric amounts of H_2O_2 as an oxidant.[8] Recently, Rios et al. reported the use of visible light in conjunction with an organic dye for the synthesis of phosphoramidates via the cross dehydrogenative coupling reactions between phosphites and amines.[9] However, these methods have one or more drawback such as long reaction time, harsh reaction conditions, low yields, use of hazardous materials and transition metals, side reactions,[10] and also in some cases they are applicable to only aromatic amines (Scheme 1).

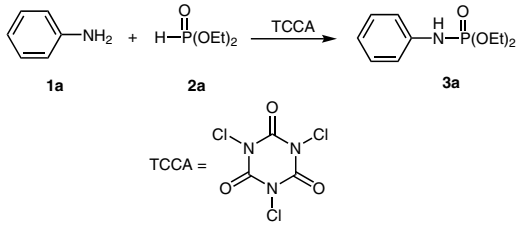


Scheme 1 Previously reported work, and this work

Trihaloisocyanuric acids are safe and stable electrophilic halogenating reagents, due to the large group of *N*-haloimides in their structures. These reagents can transfer three electrophilic halogens atoms to a substrate and at the end of the halogenations process, cyanuric acid precipitates and can be recovered from the reaction mixture. Trichloroisocyanuric acid (TCCA) is an inexpensive commercially available solid mainly reported to use for oxidation, chlorination, and dehydrogenation reactions.[11–18] To the best of our knowledge, there is no report on the synthesis of phosphoroamidates by the reaction of amines with dialkyl phosphates in the presence of TCCA in a one-pot manner. Therefore, we decided to study the feasibility of the TCCA as a safe reagent for the synthesis of phosphoroamidates under base-free conditions (Scheme 1).

Initially, the coupling reaction of diethyl phosphite (**2a**) with aniline (**1a**) was chosen as the model reaction and the experimental data for screening conditions are listed in Table 1. A mixture of 1.0 equivalent of diethyl phosphite (**2a**), 1 equivalent of aniline (**1a**), and 0.33 equivalent of TCCA was stirred in MeCN (3 mL) at room temperature for 5 hours to give **3a** in 70% yield (Table 1, entry 1). The yield of the reaction did not change on further increase of the catalyst, reaction temperature, and reaction time (entries 2–4). As shown in Table 1 (entries 5–7), after 24 hours, the coupling of **1a** with **2a** generally gave low yields in $CHCl_3$, DMF, and EtOAc compared to MeCN in the presence of TCCA (0.33 equiv).

Table 1 Reaction of Aniline (**1a**) with Diethyl Phosphite (**2a**) in the Presence of TCCA[a]

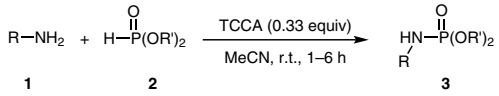


Entry	TCCA (equiv)	Solvent	Temp (°C)	Time (h)	**3a**; Yield (%)[b]
1	0.33	MeCN	r.t.	5	70
2	1	MeCN	r.t.	5	71
3	0.33	MeCN	r.t.	24	70
4	0.33	MeCN	reflux	5	66
5	0.33	$CHCl_3$	r.t.	24	42
6	0.33	DMF	r.t.	24	36
7	0.33	EtOAc	r.t.	24	50

[a] Equimolar amounts of **1a** and **2a** were used.
[b] Isolated yield.

This process was applied successfully to other amines as summarized in Table 2. Substituted anilines reacted with a mixture of diethyl phosphite and TCCA (0.33 equiv) to afford the desired products **3b–d** in moderate to good yields. Benzylamine and 2-phenethylamine as aliphatic amines also reacted with a mixture of diethyl phosphite and TCCA to give compounds **3e** and **3f** in 88 and 92% yield, respectively (Table 2, entries 5 and 6). As shown in Table 2, the reaction proceeded very well in high yield with aliphatic amines. This method was also applied to the coupling of α-naphthylamine with diethyl phosphite in the presence of TCCA (entry 7).

Table 2 Coupling Reaction of Dialkyl Phosphites with Amines[a]



Entry	**1** R	**2** R′	Product **3**	Time (h)	Yield (%)[b]
1	Ph	Et	**3a**	5	70
2	4-MeC_6H_4	Et	**3b**	4	78
3	3-$O_2NC_6H_4$	Et	**3c**	5	62
4	3-Cl-2-MeC_6H_3	Et	**3d**	6	40
5	$PhCH_2$	Et	**3e**	2	88
6	$PhCH_2CH_2$	Et	**3f**	1	92
7	α-naphthyl	Et	**3g**	4	50
8	Ph	*i*-Pr	**3h**	5	63
9	4-MeC_6H_4	*i*-Pr	**3i**	3	69

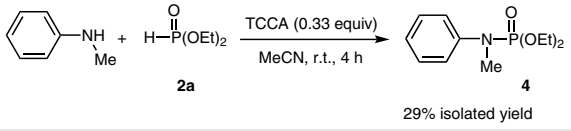
Table 2 (continued)

Entry	1 R	2 R′	Product 3	Time (h)	Yield (%)[b]
10	3-$O_2NC_6H_4$	*i*-Pr	**3j**	5	47
11	$PhCH_2$	*i*-Pr	**3k**	2	68
12	$PhCH_2CH_2$	*i*-Pr	**3l**	1	70
13	α-naphthyl	*i*-Pr	**3m**	4	22

[a] Conversions were monitored by TLC.
[b] Yields refer to the isolated pure products.

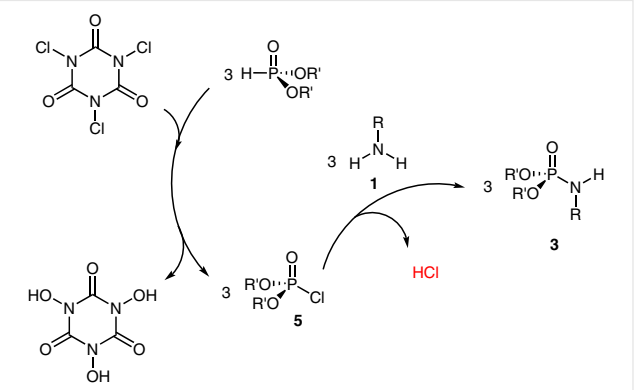
The coupling reaction of amines with a mixture diisopropyl phosphite and TCCA was also studied (Table 2, entries 8–13). The reaction of aromatic and aliphatic amines with a mixture of diisopropyl phosphite and TCCA at ambient temperature, gave the desired products **3h–m** in moderate to good yields.

It was also possible to carry out this reaction with *N*-methylaniline and the corresponding phosphoroamidate **4** was obtained in 29% yield (Scheme 2).



Scheme 2 Reaction of *N*-methylaniline with a mixture of diethyl phosphite and TCCA

A proposed mechanism is outlined in Scheme 3 for the synthesis of phosphoroamidates via the coupling of amines with dialkyl phosphite in the presence of TCCA under base-free conditions. The present process is thought to proceed via the reaction of dialkyl phosphite with TCCA to give dialkyl chlorophosphate **5**, a known intermediate, followed by nucleophilic substitution of amine with the intermediate to give the phosphoroamidate **3**. The generation of HCl gas was detected by wet pH paper test.



Scheme 3 Proposed mechanism for the synthesis of phosphoroamidates **3**

In conclusion, we have reported here the synthesis of phosphoroamidates via a coupling reaction of an amine with dialkyl phosphite in MeCN at room temperature in the presence of TCCA. It was found that TCCA is an effective reagent for this transformation. A simple workup, mild and base-free reaction conditions, moderate to good yields, and clean reaction mixtures make this method an attractive and a useful contribution to present methodologies.

All chemicals were commercial products. NMR spectra were obtained with a 400 MHz Bruker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in hertz (Hz). Silica gel column chromatography was carried out with silica gel 100 (Merck No. 10184). Merck Silica gel 60 F254 plates (No. 5744) were used for the preparative TLC. Melting points are uncorrected.

Phosphoroamidates 3; General Procedure

The required dialkyl phosphite (1.5 mmol) was added to a stirred solution of trichloroisocyanuric acid (0.116 g, 0.5 mmol) in MeCN (3 mL) and the reaction mixture was stirred for 15 min at r.t. The respective amine (1.5 mmol) was added and the mixture was stirred for 1–6 h (Table 2) at r.t. The resulting solution was diluted with aq 5% NaOH (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The pure product was obtained by column chromatography on silica gel with *n*-hexane–EtOAc (9:1 to 6:4) as eluent (Table 2).

All products gave satisfactory spectral data in accord with the assigned structures and literature reports.

Diethyl Phenylphosphoramidate (3a)

Yield: 0.240 g (70%); white solid; mp 93–95 °C (Lit.[6] mp 93 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.3 (6 H, t, J_{HH} = 6.8 Hz), 4.0–4.24 (4 H, m), 6.94 (1 H, t, J_{HH} = 7.6 Hz), 7.09 (2 H, d, J_{HH} = 5.6 Hz), 7.25 (2 H, t, J_{HH} = 7.6 Hz), 7.5 (1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.6 (d, J_{CP} = 7.0 Hz), 62.6 (d, J_{CP} = 5.0 Hz), 117.2 (d, J_{CP} = 8.0 Hz), 121.2, 129.1, 140.2.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 3.05.

Diethyl *p*-Tolylphosphoramidate (3b)

Yield: 0.283 g (78%); white solid; mp 90–92 °C (Lit.[9] mp 89–91 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (6 H, t, J_{HH} = 6.4 Hz), 2.29 (3 H, s), 4.06–4.22 (4 H, m), 6.98 (2 H, d, J_{HH} = 8.4 Hz), 7.07 (2 H, d, J_{HH} = 8.4 Hz), 7.29 (1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1 (d, J_{CP} = 7.0 Hz), 20.5, 62.5 (d, J_{CP} = 5.0 Hz), 117.2 (d, J_{CP} = 7.0 Hz), 129.7, 130.6, 137.4.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 3.15.

Diethyl (3-Nitrophenyl)phosphoramidate (3c)

Yield: 0.255 g (62%); white solid; mp 118–120 °C (Lit.[9] mp 120 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (6 H, t, J_{HH} = 7.2 Hz), 4.13–4.28 (4 H, m), 7.37–7.44 (3 H, m), 7.81 (1 H, NH), 7.93 (1 H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1 (d, J_{CP} = 6.0 Hz), 63.3 (d, J_{CP} = 5.0 Hz), 111.9 (d, J_{CP} = 7.0 Hz), 116.1, 123.3 (d, J_{CP} = 8.0 Hz), 129.9, 141.6, 149.0.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 1.58.

Diethyl (3-Chloro-2-methylphenyl)phosphoramidate (3d)

Yield: 0.165 g (40%); purple solid; mp 63–65 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (6 H, t, J_{HH} = 4 Hz), 2.343 (3 H, s), 4.05–4.20 (4 H, m), 5.38 (1 H, NH), 7.02–7.29 (3 H, m).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 13.0 (d, J_{CP} = 7.0 Hz), 63.0 (d, J_{CP} = 5.0 Hz), 116.0, 122.9, 123.8 (d, J_{CP} = 11 Hz), 127.1, 134.9, 139.2.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 1.85.

Anal. Calcd for $C_{11}H_{17}ClNO_3P$: C, 47.57; H, 6.17; N, 5.04. Found: C, 48.01; H, 6.35; N, 4.96.

Diethyl Benzylphosphoramidate (3e)[9]

Yield: 0.320 g (88%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (6 H, t, J_{HH} = 7.2 Hz), 3.69 (1 H, NH), 3.93–4.06 (6 H, m), 7.20–7.32 (5 H, m).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1 (d, J_{CP} = 7.0 Hz), 45.1, 62.2 (d, J_{CP} = 5.0 Hz), 127.2 (d, J_{CP} = 14 Hz), 128.4, 139.0 (d, J_{CP} = 6.0 Hz).

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 8.87.

Diethyl Phenethylphosphoramidate (3f)[8]

Yield: 0.355 g (92%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (6 H, t, J_{HH} = 6.8 Hz), 2.73 (2 H, t, J_{HH} = 6.8 Hz), 3.06–3.12 (2 H, m), 3.36 (1 H, NH), 3.85–3.97 (4 H, m), 7.13–7.21 (3 H, m), 7.23–7.25 (2 H, m).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1 (d, J_{CP} = 7.0 Hz), 37.9 (d, J_{CP} = 6.0 Hz), 42.7, 62.0 (d, J_{CP} = 5.0 Hz), 126.3, 128.4, 128.8, 138.9.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 9.25.

Diethyl Naphthalen-1-ylphosphoramidate (3g)

Yield: 0.210 g (50%); white solid; mp 106–108 °C (Lit.[9] mp 103–105 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.35 (6 H, t, J_{HH} = 6.4 Hz), 4.112–4.289 (4 H, m), 6.38 (1 H, NH, br, exch. D_2O), 7.41–7.58 (5 H, m), 7.87 (1 H, dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz), 8.12 (1 H, dd, J_1 = 1.2 Hz, J_2 = 8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1 (d, J_{CP} = 7.0 Hz), 62.9 (d, J_{CP} = 5.0 Hz), 114.2 (d, J_{CP} = 2.0 Hz), 120.6, 122.7, 125.5, 125.6, 125.9 (d, J_{CP} = 3.0 Hz), 126.0, 128.7, 134.3, 134.9.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 2.88.

Diisopropyl Phenylphosphoramidate (3h)

Yield: 0.243 g (63%); white solid; mp 121–123 °C (Lit.[19] mp 122–124 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (6 H, d, J_{HH} = 6.4 Hz), 1.41 (6 H, d, J_{HH} = 6.4 Hz), 4.654–4.767 (2 H, m), 6.79 (1 H, NH, br, exch. D_2O), 6.94 (1 H, t, J_{HH} = 7.6 Hz), 7.05 (2 H, d, J_{HH} = 7.6 Hz), 7.25 (2 H, m),

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7 (d, J_{CP} = 5.0 Hz), 71.5 (d, J_{CP} = 5.0 Hz), 117.3 (d, J_{CP} = 7.0 Hz), 121.0, 129.0, 140.3.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 0.36.

Diisopropyl *p*-Tolylphosphoramidate (3i)

Yield: 0.280 g (69%); white solid; mp 156–157 °C (Lit.[19] white solid).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (6 H, d, J_{HH} = 6.0 Hz), 1.40 (6 H, d, J_{HH} = 6.0 Hz), 2.29 (3 H, s), 4.66–4.74 (2 H, m), 5.91 (1 H, NH, br, exch. D_2O), 6.91 (2 H, d, J_{HH} = 8.4 Hz), 7.06 (2 H, d, J_{HH} = 8.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.5, 23.7 (d, J_{CP} = 5.0 Hz), 71.6 (d, J_{CP} = 5.0 Hz), 117.3 (d, J_{CP} = 7.0 Hz), 129.6, 130.6, 137.4.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 0.21.

Diisopropyl (3-Nitrophenyl)phosphoramidate (3j)

Yield: 0.215 g (47%); white solid; mp 105–108 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (6 H, d, J_{HH} = 6.4 Hz), 1.44 (6 H, d, J_{HH} = 6.4 Hz), 4.50–4.81 (2 H, m), 7.35–7.43 (2 H, m), 7.7 (1 H, NH, br, exch. D_2O), 7.80–7.93 (2 H, m).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7 (d, J_{CP} = 5.0 Hz), 72.4 (d, J_{CP} = 6.0 Hz), 111.8 (d, J_{CP} = 7.0 Hz), 115.8, 123.1 (d, J_{CP} = 8.0 Hz), 129.7, 141.8, 148.9.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = –0.98.

Anal. Calcd for $C_{12}H_{19}N_2O_5P$: C, 47.68; H, 6.33; N, 9.26. Found: C, 47.59; H, 6.04; N, 9.02.

Diisopropyl Benzylphosphoramidate (3k)

Yield: 0.275 g (68%); white solid; mp 48–50 °C (Lit.[19] mp 48–50 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (6 H, d, J_{HH} = 6.4 Hz), 1.38 (6 H, d, J_{HH} = 6.4 Hz), 2.95 (1 H, NH), 4.11 (2 H, d, J_{HH} = 8.4 Hz), 4.61–4.69 (2 H, m), 7.27–7.34 (5 H, m).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8 (t, J_{CP} = 4.0 Hz), 45.4, 70.9 (d, J_{CP} = 5.0 Hz), 127.3, 127.9, 128.7, 139.7 (d, J_{CP} = 7.0 Hz).

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 6.59.

Diisopropyl Phenethylphosphoramidate (3l)

Yield: 0.300 g (70%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30–1.45 (12 H, m), 2.80 (2 H, t, J_{HH} = 1.8 Hz), 2.96 (1 H, NH), 3.15–3.21 (2 H, m), 4.53–4.65 (2 H, m), 7.21–7.35 (5 H, m).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.8 (d, J_{CP} = 5.0 Hz), 37.8 (d, J_{CP} = 6.0 Hz), 42.7, 70.7 (d, J_{CP} = 5.0 Hz), 126.3, 128.6, 128.9, 138.7.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 7.13.

Anal. Calcd for $C_{14}H_{24}NO_3P$: C, 58.93; H, 8.47; N, 4.91. Found: C, 59.10; H, 8.16; N, 4.84

Diisopropyl Naphthalen-1-ylphosphoramidate (3m)

Yield: 0.104 g (22%); white solid; mp 148–152 °C (Lit.[19] white solid).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (6 H, d, J_{HH} = 6 Hz), 1.43 (6 H, d, J_{HH} = 6 Hz), 4.71–4.82 (2 H, m), 5.91 (1 H, NH), 7.39–7.57 (5 H, m), 7.87–7.98 (2 H, m).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7 (d, J_{CP} = 5.0 Hz), 71.9 (d, J_{CP} = 4.0 Hz), 113.9, 120.1, 122.2, 125.0, 125.1, 125.8 (d, J_{CP} = 5.0 Hz), 125.9 (d, J_{CP} = 5.0 Hz), 128.8, 134.2, 135.0.

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 0.31.

Diethyl *N*-Methyl-*N*-phenylphosphoramidate (4)[8]

Yield: 0.105 g (29%); yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (6 H, t, J_{HH} = 6.4 Hz), 3.21 (3 H, d, J_{HH} = 8.4 Hz), 3.98–4.17 (4 H, m), 7.05–7.09 (1 H, m), 7.27–7.33 (4 H, m).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.0 (d, J_{CP} = 7.0 Hz), 36.8 (d, J_{CP} = 5.0 Hz), 62.5 (d, J_{CP} = 5.0 Hz), 121.8 (d, J_{CP} = 4.0 Hz), 123.5, 128.9, 144.1 (d, J_{CP} = 4.0 Hz).

^{31}P NMR ($CDCl_3$, H_3PO_4): δ = 5.90.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589111.

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