Direct Oxidative C–P Bond Formation of Indoles with Dialkyl Phosphites

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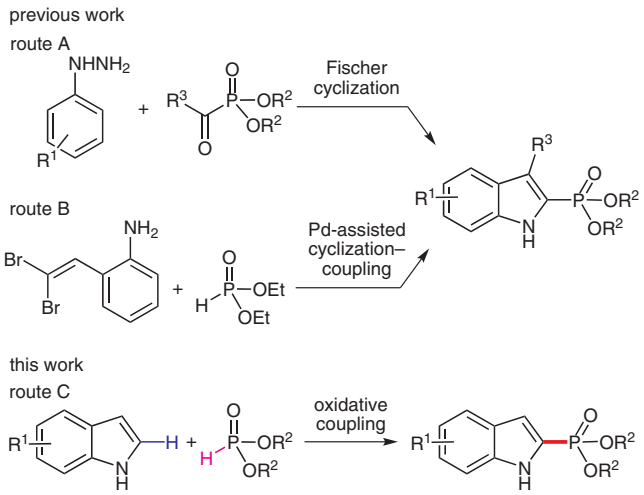
Abstract: The direct phosphonation of indoles was developed. In this reaction, dialkyl phosphites and indoles were used as substrates, and the C–P bond was formed through oxidative coupling mediated by silver(I) acetate. Various indoles and different dialkyl phosphites were effective substrates for the reaction, and dialkylphosphoryl-substituted indoles were obtained in up to 71% yield.

Key words: indole, dialkyl phosphite, phosphonation, silver acetate, oxidative coupling

Aryl and heteraryl phosphites are important chemicals in organic synthesis, medicinal chemistry, and nucleic acid chemistry.[1] Several methods based on established reactions have been developed for the synthesis of dialkyl arylphosphonates over the last decade; the Michaelis–Arbuzov reaction has been frequently used.[2] Since the reported palladium-catalyzed coupling of aryl and vinyl bromides in 1980s by Hirao and co-workers,[3] various methods for the transition-metal-catalyzed (such as Pd, Cu, and Ni) cross-coupling reactions of aryl halides and phosphonates have been developed.[4] Worthy of note is a new method of C–P bond by palladium-catalyzed oxidative coupling of arylboronic acids or aryltrifluoroborates with phosphonates developed by Larhed;[5a] a similar reaction catalyzed by copper was recently reported by Fang and co-workers.[5b] On the other hand, the direct phosphonation of arenes or hetarenes is a powerful and efficient tool that gives easy access to arylphosphonates. Fields,[6a] Effenberger,[6b,c] and Zhang[6d] have reported the synthesis of arylphosphonates by direct phosphonation using *tert*-butyl peroxide, ammonium cerium(IV) nitrate, sodium persulfate/silver nitrate, or manganese(III). Significant progress was achieved by Ishii and co-workers,[7] who utilized the manganese(II) acetate/cobalt(II) acetate-catalyzed direct C–P bond formation of arenes through a C–H bond-activation reaction. However, to the best of our knowledge, the first example of direct phosphonation of hetarenes was reported by Zhang and co-workers in 2006.[8]

As potential biologically active chemicals, indolylphosphonates are accessible by only a few routes. Fischer cyclization (Scheme 1, route A) is the predominate method, which has been used by several groups for the synthesis of indolylphosphonates.[9] In 2004, Eustache developed a new method for the synthesis of indolylphosphonates utilizing a palladium-assisted cyclization–coupling reaction[10] (Scheme 1, route B). However, multiple steps were necessary for the synthesis of substrates and harsh conditions were involved. We surmised that these problems can be circumvented by instead using the direct phosphonation of indoles. Herein, we describe a new method for the synthesis of indolylphosphonates in one step via direct oxidative coupling oxidized by silver(I) acetate (Scheme 1, route C).

To identify suitable conditions for the direct phosphonation of indoles, the coupling of 1*H*-indole (**1a**) and diethyl phosphite (**2a**) was chosen as a model reaction. Initially using silver(I) acetate as the oxidant and 1,2-dichloroethane as the solvent gave the desired product **3aa** in 44% yield (Table 1, entry 1). When other silver oxidants were used under the same conditions, **3aa** was obtained in lower yields (entries 2 and 3). To our surprise, using manganese(III) acetate as the oxidant, which has proved to be efficient for the phosphonation of pyrroles,[8] gave **3aa** in a lower, 28%, yield (entry 4). It was also disappointing that other oxidants were completely ineffective in the oxidative coupling of **1a** and **2a** (entries 5–7). Although several transition metals such as copper, iron, palladium, and rhodium were added, no improvement in the efficiency of the reaction resulted.[11] In the next stage, the influence of the solvent was examined on the silver(I) acetate catalyzed reaction. In comparison to the reaction in 1,2-dichloroethane, the use of solvents such as 1,4-dioxane, toluene, ethanol and acetonitrile gave **3aa** in lower yields (entries 8–11). The use of *N*,*N*-dimethylformamide or dimethyl sulfoxide as the solvent gave only trace amounts



Scheme 1 Methods for the synthesis of indolylphosphonates

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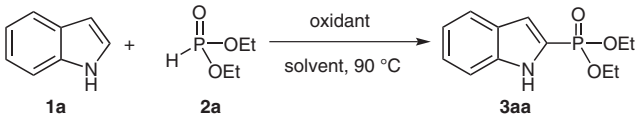
of difficult to separate products (entries 12 and 13). To improve the efficiency of the reaction, the addition of various acids, which were used to activate the substrate in previous work,[12] to the reaction was examined, but disappointingly this had no influence on the yield of the product.[11]

Using the optimized reaction conditions, various substituted indoles **1a–f** were reacted with dialkyl phosphites **2a–c** (Table 2). In general, indoles **1a–f** were readily converted into the corresponding indolylphosphonates **3ac–ec** in moderate to good yields. Indoles bearing either an electron-donating group **1b** or an electron-withdrawing group **1c** readily reacted with dialkyl phosphites **2a–c**, albeit with lower yields compared indole **1a** (entries 4–9 vs. entries 1–3). Sterically hindered 3-methyl-1*H*-indole (**1d**) was also converted into the desired indolylphosphonates **3da–dc** in moderate yields (entries 10–12). Interestingly, a small amount of 3-phosphonation indole products, **4ea**, **4eb**, and **4ec**, were obtained when 1-methyl-1*H*-indole (**1e**) was used as the substrate (entries 13–15). Importantly, when 2-methyl- and 2-phenyl-1*H*-indole (**1f**) were used as substrates, 2-methyl-1*H*-indole gave no product whereas 2-phenyl-1*H*-indole (**1f**) was phosphonated to afford **4fa** in good yield (entry 16).

The mechanism of the reaction, however, remains unclear. Based on the influence of the electron-withdrawing and electron-donating groups, a radical process was proposed as the phosphonation reaction pathway. This hypothesis was supported by the regioselectivity of this reaction and the outcome of the reaction of phosphite **2a** with 2-phenyl-1*H*-indole (**1f**) (entry 16). To further confirm the radical intermediate in the reaction, the radical inhibitor butylated hydroxytoluene (BHT) was added to the reaction of **1a** and **2a**, and none of the desired product **3aa** was obtained. As shown in Scheme 2, dialkyl phosphite is initially oxidized to radical **5** by silver(I) acetate, sequential addition of **5** to indole **1a** affords the intermediate **6**, which is then converted into the desired product **3aa** by oxidation with silver(I) acetate.

In conclusion, indoles were, for the first time, successfully phosphonated by C–P bond formation through direct oxidative coupling using silver(I) acetate. A wide variety of indoles and dialkyl phosphites participated in the reaction to afford the desired indolylphosphonates in up to 71% yield. Efforts to improve the efficiency of the reaction and confirm the mechanism are in progress.

Table 1 Optimization of the Reaction Conditions[a]



1a 2a 3aa

Entry	Oxidant	Solvent	Yield[b] (%)
1	AgOAc	DCE	44
2	Ag_2CO_3	DCE	24
3	Ag_2O	DCE	23
4	Mn(OAc)3	DCE	28
5	BQc	DCE	–
6	DDQ	DCE	–
7	$PhI(OAc)_2$	DCE	–
8	AgOAc	1,4-dioxane	27
9	AgOAc	toluene	39
10	AgOAc	EtOH	35
11	AgOAc	MeCN	19
12	AgOAc	DMSO	–
13	AgOAc	DMF	–

[a] Reaction conditions: indole **1a** (0.5 mmol), phosphite **2a** (0.25 mmol), oxidant (0.75 mmol), 90 °C, 24 h.
[b] Isolated yields.
[c] BQ = 1,4-benzoquinone.

All substrates were purchased from Sigma-Aldrich and used without further purification. Flash column chromatography was performed using 300–400 mesh silica gel with the indicated solvent system according to standard techniques. Nuclear magnetic resonance spectra were recorded on Bruker DRX-500 MHz spectrometers. High-resolution mass spectra were performed on a Micromass HPLC Q-TOF mass spectrometer.

Dialkoxyphosphoryl-Substituted Indoles 3 and 4; General Procedure

Indole **1** (0.5 mmol) and AgOAc (0.75 mmol) were weighed under air and placed in a 1-dram vial with a Teflon cap and sealed. Subsequently, the tube was evacuated and back filled with argon (3 cycles). Diethyl phosphite **2** (0.25 mmol) and CH_2Cl_2 (2 mL) were added under an argon atmosphere, and the cap was sealed. After heated in an oil bath at 90 °C for 24 h, CH_2Cl_2 (5 mL) was added to dilute the mixture. The mixture was filtered through Celite, and the solvent was distilled under vacuum. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2–acetone, 30:1 to 10:1) to give the desired product.

2-(Diethoxyphosphoryl)-1*H*-indole (3aa)

White solid; yield: 27.9 mg (44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.44 (s, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.52 (d, *J* = 8.3 Hz, 1 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.17–7.10 (m, 1 H), 7.06–7.01 (m, 1 H), 4.26–4.07 (m, 4 H), 1.34 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.62 (d, *J* = 13.0 Hz), 127.63 (d, *J* = 16.0 Hz), 124.97 (s), 124.61 (s), 122.79 (s), 121.92 (d, *J* = 1.0 Hz), 112.49 (d, *J* = 2.0 Hz), 111.73 (d, *J* = 17.0 Hz), 63.03 (d, *J* = 5.0 Hz), 16.46 (d, *J* = 7.0Hz).

^{31}P NMR (160 MHz, $CDCl_3$): δ = 11.17.

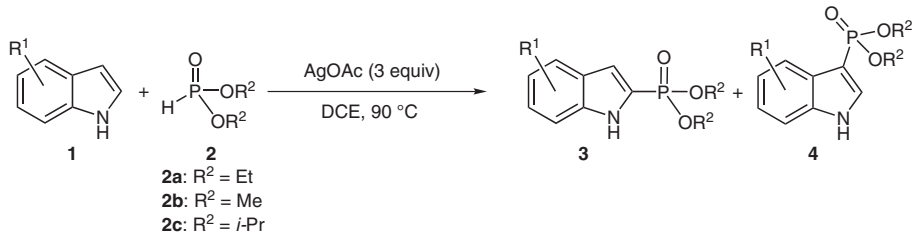
HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{16}NNaO_3P$: 276.0766; found: 276.0762.

2-(Dimethoxyphosphoryl)-1*H*-indole (3ab)

Pale yellow solid; yield: 25.0 mg (44%).

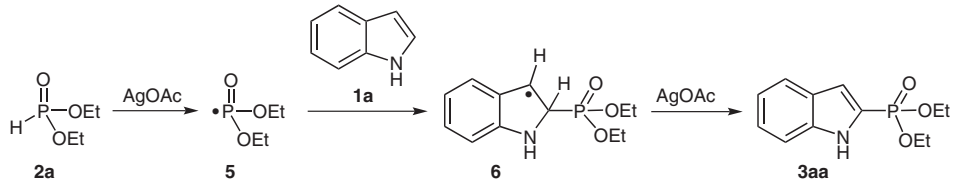
^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.35 (s, 1 H), 7.70–7.66 (m, 1 H), 7.52 (dd, *J* = 8.3, 0.8 Hz, 1 H), 7.34–7.27 (m, 1 H), 7.15 (ddd,

Table 2 Phosphonation of Indoles[a]



Entry	Indole	R^1	Phosphite	R^2	Products	Ratio **3/4**	Yields[b] (%)
1	**1a**	H	**2a**	Et	**3aa**	>99:1	44
2	**1a**	H	**2b**	Me	**3ab**	>99:1	44
3	**1a**	H	**2c**	i-Pr	**3ac**	>99:1	37
4	**1b**	5-OMe	**2a**	Et	**3ba**	>99:1	34
5	**1b**	5-OMe	**2b**	Me	**3bb**	>99:1	37
6	**1b**	5-OMe	**2c**	*i*-Pr	**3bc**	>99:1	19
7	**1c**	5-CO_2Me	**2a**	Et	**3ca**	>99:1	22
8	**1c**	5-CO_2Me	**2b**	Me	**3cb**	>99:1	18
9	**1c**	5-CO_2Me	**2c**	*i*-Pr	**3cc**	>99:1	24
10	**1d**	3-Me	**2a**	Et	**3da**	>99:1	71
11	**1d**	3-Me	**2b**	Me	**3db**	>99:1	53
12	**1d**	3-Me	**2c**	*i*-Pr	**3dc**	>99:1	37
13	**1e**	1-Me	**2a**	Et	**3ea/4ea**	15:1	39
14	**1e**	1-Me	**2b**	Me	**3eb/4eb**	20:1	44
15	**1e**	1-Me	**2c**	*i*-Pr	**3ec/4ec**	20:1	29
16	**1f**	2-Ph	**2a**	Et	**4fa**	<1:99	71

[a] Reaction conditions: indole (0.5 mmol), phosphite (0.25 mmol), AgOAc (0.75 mmol), DCE (2 mL), 90 °C, 24 h.
[b] Isolated yields.
[c] The ratio of major and minor products.



Scheme 2 Possible mechanism for the phosphonation of indole

J = 7.9, 7.1, 0.8 Hz, 1 H), 7.06 (ddd, *J* = 4.2, 2.0, 0.8 Hz, 1 H), 3.81 (d, *J* = 11.5 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.75 (d, *J* = 13.0 Hz), 127.60 (d, *J* = 15.6 Hz), 124.87 (s), 123.10 (s), 122.00 (s), 121.35 (s), 120.80 (s), 112.66 (s), 112.36 (d, *J* = 17.5 Hz), 53.42 (d, *J* = 5.2 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 13.86 (s).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{10}H_{12}NNaO_3P$: 248.0453; found: 248.0449.

2-(Diisopropoxyphosphoryl)-1*H*-indole (3ac)
Pale yellow solid; yield: 26.2 mg (37%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.31 (s, 1 H), 7.70–7.65 (m, 1 H), 7.51 (dd, *J* = 8.3, 0.7 Hz, 1 H), 7.28 (dd, *J* = 7.9, 7.3 Hz, 1 H), 7.16–7.11 (m, 1 H), 7.02 (ddd, *J* = 4.3, 2.0, 0.8 Hz, 1 H), 4.77–4.67 (m, 2 H), 1.39 (d, *J* = 6.2 Hz, 6 H), 1.26 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.45 (d, *J* = 12.8 Hz), 127.78 (d, *J* = 15.5 Hz), 126.58 (s), 124.83 (s), 124.41 (s), 121.95 (s), 120.55 (s), 112.41 (s), 111.38 (d, *J* = 16.9 Hz), 71.81 (d, *J* = 5.1 Hz), 24.30 (d, *J* = 3.7 Hz), 23.97 (d, *J* = 5.1 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 8.48 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}NO_3NaP$: 304.1079; found: 304.1072.

2-(Diethoxyphosphoryl)-5-methoxy-1*H*-indole (3ba)
Pale yellow solid; yield: 24.0 mg (34%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.98 (s, 1 H), 7.39 (d, *J* = 8.9 Hz, 1 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 7.00–6.93 (m, 2 H), 4.24–4.04 (m, 4 H), 3.85 (s, 3 H), 1.33 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.86 (s), 133.91 (d, *J* = 13.0 Hz), 128.05 (d, *J* = 15.4 Hz), 125.18 (s), 123.43 (s), 116.22 (s), 113.22 (s), 111.35 (d, *J* = 17.2 Hz), 102.26 (s), 62.97 (d, *J* = 5.0 Hz), 55.94 (s), 16.47 (d, *J* = 6.7 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 10.69 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}NNaO_4P$: 306.0871; found: 306.0867.

2-(Dimethoxyphosphoryl)-5-methoxy-1*H*-indole (3bb)
Pale yellow solid; yield: 23.5 mg (37%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.18 (s, 1 H), 7.41 (d, *J* = 8.9 Hz, 1 H), 7.08 (d, *J* = 2.3 Hz, 1 H), 7.01–6.94 (m, 2 H), 3.84 (s, 3 H), 3.80 (d, *J* = 11.5 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.90 (s), 134.12 (d, *J* = 13.2 Hz), 127.97 (d, *J* = 15.8 Hz), 123.40 (s), 121.64 (s), 116.46 (s), 113.31 (s), 111.81 (d, *J* = 17.3 Hz), 102.20 (s), 55.93 (s), 53.37 (d, *J* = 5.1 Hz), 29.89 (s).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 13.79 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}NNaO_4P$: 278.0558; found: 278.0562.

2-(Diisopropoxyphosphoryl)-5-methoxy-1*H*-indole (3bc)
Pale yellow solid; yield: 14.4 mg (19%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.96 (s, 1 H), 7.38 (d, *J* = 8.9 Hz, 1 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 6.99–6.92 (m, 2 H), 4.76–4.65 (m, 2 H), 3.85 (s, 3 H), 1.38 (d, *J* = 6.2 Hz, 6 H), 1.26 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.78 (s), 133.75 (d, *J* = 12.9 Hz), 128.15 (d, *J* = 15.4 Hz), 126.96 (s), 125.21 (s), 115.93 (s), 113.15 (s), 110.95 (d, *J* = 17.1 Hz), 102.32 (s), 71.74 (d, *J* = 5.1 Hz), 55.94 (s), 24.30 (d, *J* = 3.8 Hz), 23.98 (d, *J* = 5.1 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 8.35 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NNaO_4P$: 334.1184; found: 334.1177.

Methyl 2-(Diethoxyphosphoryl)-1*H*-indole-5-carboxylate (3ca)
Pale yellow solid; yield: 17.1 mg (22%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.86 (s, 1 H), 8.46 (d, *J* = 0.7 Hz, 1 H), 7.98 (dd, *J* = 8.7, 1.0 Hz, 1 H), 7.53 (d, *J* = 8.7 Hz, 1 H), 7.12 (dd, *J* = 4.3, 1.1 Hz, 1 H), 4.26–4.12 (m, 4 H), 3.94 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.02 (s), 141.00 (d, *J* = 12.6 Hz), 127.22 (d, *J* = 15.5 Hz), 126.74 (s), 125.61 (s), 125.26 (s), 122.92 (s), 112.95 (d, *J* = 16.6 Hz), 112.26 (s), 63.32 (d, *J* = 5.3 Hz), 52.14 (s), 16.47 (d, *J* = 6.6 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 9.78 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}NNaO_5P$: 334.0820; found: 334.0818.

Methyl 2-(Dimethoxyphosphoryl)-1*H*-indole-5-carboxylate (3cb)
Pale yellow solid; yield: 12.6 mg (18%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.51 (s, 1 H), 8.47 (d, *J* = 0.7 Hz, 1 H), 8.00 (dd, *J* = 8.7, 1.3 Hz, 1 H), 7.53 (d, *J* = 8.7 Hz, 1 H), 7.14 (d, *J* = 3.8 Hz, 1 H), 3.94 (s, 3 H), 3.84 (d, *J* = 11.5 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.94 (s), 140.99 (d, *J* = 12.6 Hz), 127.20 (d, *J* = 15.6 Hz), 125.89 (s), 125.34 (s), 123.14 (s), 113.58 (d, *J* = 16.7 Hz), 112.22 (s), 53.60 (d, *J* = 5.3 Hz), 52.18 (s).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 12.61 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}NNaO_5P$: 306.0508; found: 306.0507.

Methyl 2-(Diisopropoxyphosphoryl)-1*H*-indole-5-carboxylate (3cc)
Pale yellow solid; yield: 20.7 mg (24%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.03 (s, 1 H), 8.46 (s, 1 H), 7.98 (dd, *J* = 8.7, 1.0 Hz, 1 H), 7.53 (d, *J* = 8.7 Hz, 1 H), 7.09 (dd, *J* = 4.3, 1.2 Hz, 1 H), 4.81–4.70 (m, 2 H), 3.94 (s, 3 H), 1.40 (d, *J* = 6.2 Hz, 6 H), 1.29 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.08 (s), 140.93 (d, *J* = 12.7 Hz), 128.47 (s), 127.29 (d, *J* = 15.5 Hz), 126.72 (s), 125.30 (d, *J* = 18.7 Hz), 122.74 (s), 112.48 (d, *J* = 16.6 Hz), 112.22 (s), 72.19 (d, *J* = 5.3 Hz), 52.10 (s), 24.27 (d, *J* = 3.8 Hz), 23.96 (d, *J* = 5.0 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 7.48 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{22}NNaO_5P$: 362.1133; found: 362.1128.

2-(Diethoxyphosphoryl)-3-methyl-1*H*-indole (3da)
Pale yellow solid; yield: 47.1 mg (71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.51 (s, 1 H), 7.66–7.62 (m, 1 H), 7.44 (d, *J* = 8.3 Hz, 1 H), 7.30 (dd, *J* = 8.0, 7.3 Hz, 1 H), 7.17–7.12 (m, 1 H), 4.17 (ddq, *J* = 14.3, 10.1, 7.1 Hz, 2 H), 4.06 (ddq, *J* = 10.1, 8.3, 7.1 Hz, 2 H), 2.50 (d, *J* = 2.0 Hz, 3 H), 1.32 (q, *J* = 6.9 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.06 (d, *J* = 12.8 Hz), 128.51 (d, *J* = 16.4 Hz), 124.95 (s), 121.97 (d, *J* = 17.6 Hz), 120.24 (s), 120.01 (s), 119.44 (s), 117.70 (s), 112.25 (s), 52.85 (d, *J* = 4.7 Hz), 9.56 (s).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 12.09 (d, *J* = 5.8 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}NNaO_3P$: 290.0922; found: 290.0918.

2-(Dimethoxyphosphoryl)-3-methyl-1*H*-indole (3db)
Pale yellow solid; yield: 31.8 mg (53%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.47 (d, *J* = 8.3 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.14 (t, *J* = 7.5 Hz, 1 H), 3.77 (d, *J* = 11.6 Hz, 6 H), 2.50 (d, *J* = 2.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.89 (d, *J* = 12.8 Hz), 128.34 (d, *J* = 16.4 Hz), 124.78 (s), 121.80 (d, *J* = 17.6 Hz), 120.07 (s), 119.84 (s), 119.27 (s), 117.53 (s), 112.08 (s), 52.67 (d, *J* = 4.7 Hz), 9.39 (s).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 15.51 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}NNaO_3P$: 262.0609; found: 262.0609.

2-(Diisopropoxyphosphoryl)-3-methyl-1*H*-indole (3dc)
Pale yellow solid; yield: 27.5 mg (37%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.61 (s, 1 H), 7.63 (dd, *J* = 8.0, 0.6 Hz, 1 H), 7.45 (d, *J* = 8.3 Hz, 1 H), 7.28 (dd, *J* = 7.9, 7.2 Hz, 1 H), 7.16–7.11 (m, 1 H), 4.70–4.63 (m, 2 H), 2.50 (d, *J* = 2.0 Hz, 3 H), 1.40 (d, *J* = 6.2 Hz, 6 H), 1.20 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.59 (d, *J* = 12.7 Hz), 128.75 (d, *J* = 16.2 Hz), 124.52 (s), 122.62 (s), 121.00–120.45 (m), 120.17 (s), 119.81 (s), 112.17 (s), 71.37 (d, *J* = 4.7 Hz), 24.32 (d, *J* = 3.8 Hz), 23.87 (d, *J* = 5.1 Hz), 9.85 (s).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 9.49 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NNaO_3P$: 318.1235; found: 318.1235.

2-(Diethoxyphosphoryl)-1-methyl-1*H*-indole (3ea) and 3-(Diethoxyphosphoryl)-1-methyl-1*H*-indole (4ea)
Pale yellow liquid; yield: 26.3 mg (39%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.0 Hz, 1 H), 7.40–7.31 (m, 2 H), 7.19–7.13 (m, 2 H), 4.24–4.10 (m, 4 H), 3.95 (s, 3 H), 1.35 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.29 (d, *J* = 12.3 Hz), 127.33 (s), 126.73 (d, *J* = 15.6 Hz), 125.60 (s), 124.71 (s), 122.34 (s), 120.46 (s), 114.26 (d, *J* = 17.4 Hz), 110.15 (d, *J* = 1.9 Hz), 62.83 (d, *J* = 5.3 Hz), 31.99 (s), 16.49 (d, *J* = 6.5 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 10.01 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}NNaO_3P$: 290.0922; found: 290.0914.

2-(Dimethoxyphosphoryl)-1-methyl-1*H*-indole (3eb) and 3-(Dimethoxyphosphoryl)-1-methyl-1*H*-indole (4eb)
Pale yellow liquid, 26.4 mg (44%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.0 Hz, 1 H), 7.40–7.32 (m, 2 H), 7.20–7.13 (m, 2 H), 3.94 (s, 3 H), 3.81 (d, *J* = 11.4 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.37 (d, *J* = 12.4 Hz), 126.70 (d, *J* = 15.7 Hz), 125.84 (s), 124.89 (s), 124.10 (s), 122.37 (s), 120.56 (s), 114.68 (d, *J* = 17.3 Hz), 110.21 (s), 53.24 (d, *J* = 5.4 Hz), 31.98 (s).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 13.03 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}NNaO_3P$: 262.0609; found: 262.0603.

2-(Diisopropoxyphosphoryl)-1-methyl-1*H*-indole (3ec) and 3-(Diisopropoxyphosphoryl)-1-methyl-1*H*-indole (4ec)
Pale yellow liquid, 21.0 mg (29%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.0 Hz, 1 H), 7.34 (dt, *J* = 8.4, 7.6 Hz, 2 H), 7.18 (dd, *J* = 4.5, 0.6 Hz, 1 H), 7.14 (ddd, *J* = 7.9, 6.7, 1.2 Hz, 1 H), 4.80–4.70 (m, 2 H), 3.94 (s, 3 H), 1.39 (d, *J* = 6.2 Hz, 6 H), 1.27 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.20 (d, *J* = 12.1 Hz), 128.97 (s), 127.24 (s), 126.79 (d, *J* = 15.7 Hz), 124.50 (s), 122.33 (s), 120.35 (s), 113.96 (d, *J* = 17.5 Hz), 110.09 (s), 71.59 (d, *J* = 5.4 Hz), 32.01 (s), 24.32 (d, *J* = 3.9 Hz), 23.98 (d, *J* = 4.9 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 7.57 (s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NNaO_3P$: 318.1235; found: 318.1229.

3-(Diethoxyphosphoryl)-2-phenyl-1*H*-indole (3fa)
Pale yellow solid; yield: 58.1 mg (71%).

^{1}H NMR (400 MHz, DMSO): δ = 12.17 (s, 1 H), 7.93 (d, *J* = 7.9 Hz, 1 H), 7.77 (d, *J* = 7.4 Hz, 2 H), 7.50 (dd, *J* = 14.9, 7.2 Hz, 4 H), 7.19 (dt, *J* = 24.0, 7.3 Hz, 2 H), 4.01–3.77 (m, 4 H), 1.07 (t, *J* = 7.0 Hz, 6 H).

13C NMR (101 MHz, DMSO): δ = 145.89 (s), 145.66 (s), 136.81 (d, *J* = 15.0 Hz), 132.24 (s), 130.51 (d, *J* = 13.2 Hz), 130.08 (s), 129.42 (s), 128.53 (s), 122.96 (s), 121.38 (d, *J* = 14.5 Hz), 112.25 (s), 98.09 (s), 95.96 (s), 61.30 (d, *J* = 5.1 Hz), 16.49 (d, *J* = 6.8 Hz).

^{31}P NMR (160 MHz, DMSO): δ = 17.21 (m).

HRMS (ESI): *m*/*z* [M] calcd for $C_{18}H_{20}NO_3P$: 329.1181; found: 329.1183.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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