Facile P,N-heterocycle synthesis *via* tandem aminomethylation–cyclization of *H*-phosphinate building blocks†

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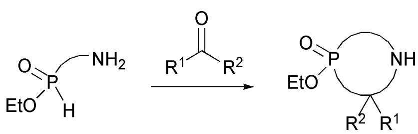
Various heterocycles containing phosphorus and nitrogen are easily synthesized from readily available *H*-phosphinate building blocks. Aminomethylation of these *H*-phosphinates is followed by *in situ* cyclization through substitution or cross-coupling to produce novel heterocycles in moderate to good yields.

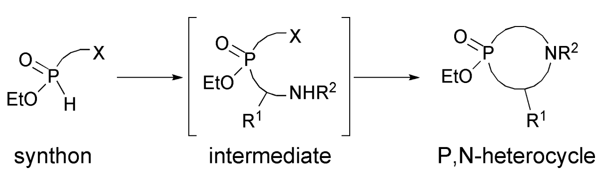
Introduction

Perhaps surprisingly, few phosphorus–nitrogen heterocycles have been synthesized previously.[1] In recent work, we reported the formation of such heterocycles starting from ω-amino-*H*-phosphinates (eqn (1)) through condensation with carbonyl compounds.[2] The method was made possible by synthetic methodologies we developed to access the starting materials.[3] Herein, we shifted the focus to precursors which do not contain an amino group, but instead possess a reactive halide.



(1)

With the exception of our previous report (eqn (1)),[2] P,N-containing phosphinic heterocycles are rare in the literature. Since heterocycles have shown a variety of biological activities, and since cyclic P,N-phosphinates can be considered analogs of amino acids, we set out to expand the range of compounds accessible from simple building blocks. Below, we describe a general approach to P,N-heterocycles based on the Kabachnick–Fields aminomethylation[4] of precursors, followed by *in situ* cyclization of the resulting amines (Scheme 1). Over the past several years, our laboratory has reported several general methods to prepare functionalized *H*-phosphinates.[3] In the present work, such intermediates are prepared and their use in the synthesis of P,N-heterocycles is investigated.



Scheme 1 Strategy for the synthesis of P,N-heterocycles

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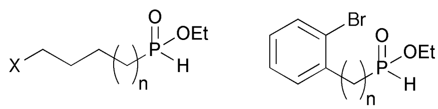
Results and discussion

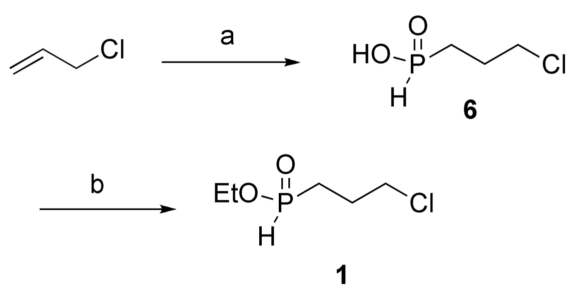
Precursor synthesis



1 n = 0, X = Cl
2 n = 1, X = Br

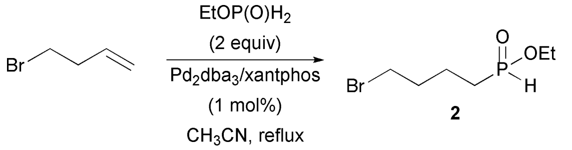
3 n = 0
4 n = 1
5 n = 2

Several synthons were prepared through established reactions.[3] Compounds **1**, **2** and **5** were prepared *via* hydrophosphinylation,[3d–j] compound **3** *via* Pd-catalyzed cross-coupling,[3k] and compound **4** *via* base-promoted alkylation.[3r] The detailed conditions are shown in Schemes 2–4, and eqn (2) and (3). Synthon **1** (Scheme 2) was synthesized through our radical hydrophosphinylation using Et_3B as the initiator, as reported previously.[3h] The resulting intermediate **6** was esterified[5] directly to produce ester **1**. The low yield of compound **1** was attributed to difficulties during the purification of this polar compound using chromatography on silica gel. Nonetheless, the preparation of **1** was easily accomplished.



Scheme 2 Synthesis of ethyl (3-chloropropyl)-*H*-phosphinate **1**. (a) NaH_2PO_2, Et_3B, rt, 2 h, 71%; (b) $(EtO)_4Si$, toluene, reflux, 24 h, 40%.

Homolog **2** was prepared in a single step through palladium-catalyzed hydrophosphinylation[3d] of 4-bromo-1-butene (eqn (2)). Synthon **2** was obtained in 67% yield. A similar reaction was used to prepare **5** from commercially available 2-bromostyrene (eqn (3)) in 64% yield.



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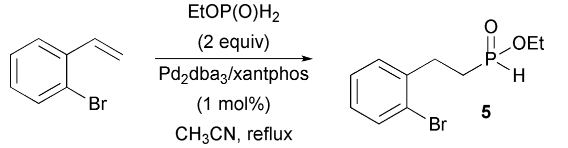
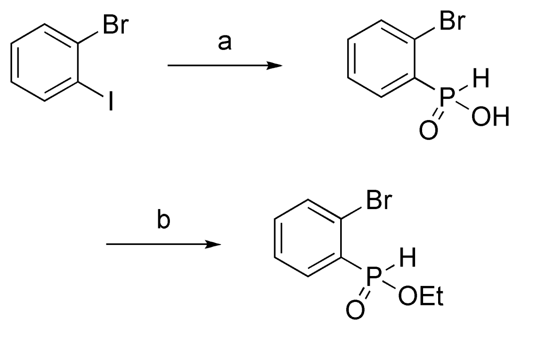


(3)

Synthon **3** required the use of our palladium-catalyzed cross-coupling of anilinium hypophosphite[3k] with 1-bromo-2-iodobenzene. Esterification then proceeded in reasonable yield to form **3** (Scheme 3).



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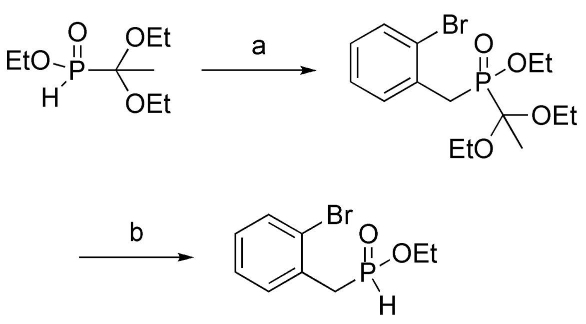
Scheme 3 Synthesis of ethyl (2-bromophenyl)-*H*-phosphinate **3**. (a) 1-bromo-2-iodobenzene, anilinium hypophosphite (3 equiv.), $Pd(OAc)_2$ (2 mol%), dppp (2.2 mol%), CH_3CN, reflux, 16 h, 65%; (b) $(EtO)_4Si$, toluene, reflux, 24 h, 64%.

Finally, synthon **4** was synthesized through the LiHMDS-promoted alkylation[3r] of 2-bromobenzyl bromide followed by deprotection of the acetal using TMSCl.[6] The sequence produced **4** in 60% overall yield (Scheme 4).



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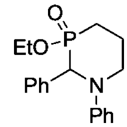
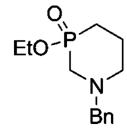
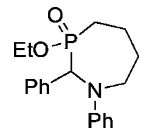
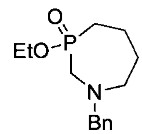
Scheme 4 Synthesis of ethyl (2-bromobenzyl)-*H*-phosphinate **4**. (a) 2-bromobenzyl bromide, LiHMDS, THF, −78 °C to rt, 3 h, 61%; (b) TMSCl, CH_2Cl_2, EtOH, rt, 16 h, 99%.

Reactivity and cyclization

With the above precursors in hand, their reactions with imines were investigated. Table 1 shows the results obtained with synthons **1** and **2**. Reaction of the *H*-phosphinates with imines proceeded smoothly and cyclization then took place uneventfully.

Table 1 P,N-heterocycle formation from **1** and **2**

Entry	Synthon	Imine[a]	Product	Isolated yield (%)[b]
1	**1**	PhCH=NPh		61
2	**1**	H_2C=NBn		58
3	**2**	PhCH=NPh		76
4	**2**	H_2C=NBn		45

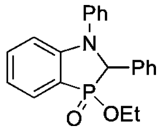
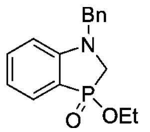
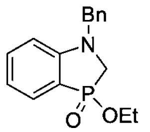
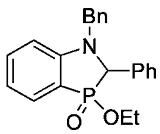
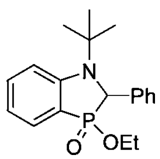
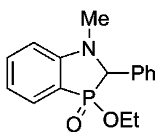
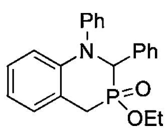
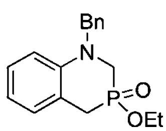
[a] Conditions: *N*-benzylideneaniline, toluene, reflux, 16 h; or 1,3,5-tribenzylhexahydro-1,3,5-triazine, toluene, reflux, 16 h. [b] Yield of pure compound after column chromatography.

The reactions of 2-bromophenyl-substituted *H*-phosphinate esters were investigated next (Table 2). Compounds **3** and **4** were subjected to similar reaction conditions, except that a base (Cs_2CO_3, 1.5 equiv.) and a palladium catalyst ($Pd(PPh_3)_4$, 2 mol%) were also added to the reaction mixtures. As expected, the aminomethylation took place easily, but, perhaps more surprisingly, the simplest Pd-catalyst delivered C–N bond formation in good yield, without the need for more sophisticated Buchwald–Hartwig-type cross-coupling catalysts.[7] Thus, 5- and 6-membered P,N-heterocycles were obtained in a one-pot procedure (Table 2). Compound **3** reacted with a variety of imines (Table 2, entries 1–6). Interestingly, a reaction (entry 3) conducted with *in situ* formation of the imine (from paraformaldehyde and benzylamine) gave the expected product in only slightly lower yield than with the triazine precursor (entry 2). Compound **4** provided the 6-membered heterocycle in comparable yields (entries 7 and 8). Again, $Pd(PPh_3)_4$ successfully catalyzed the cross-coupling step.

However, with synthon **5**, although the Kabachnik–Fields reaction took place in good yield, the resulting intermediates did not cyclize to give the 7-membered ring under otherwise identical conditions. The aminomethylated products were obtained with *N*-benzylideneaniline or 1,3,5-tribenzylhexahydro-1,3,5-triazine in 51 and 67% isolated yields, respectively.

In a different (but related) approach, the heterocyclization of unsaturated ethyl cinnamyl-*H*-phosphinate was investigated through a tandem aminomethylation–Heck cyclization process (Scheme 5). Readily available cinnamyl-*H*-phosphinic acid[8] **7** was esterified[5] to **8** using our typical conditions. Ester **8** was then reacted with 2-iodoaniline and paraformaldehyde to form

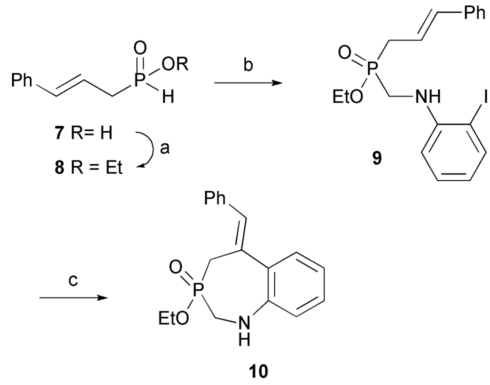
Table 2 P,N-heterocycle formation from **3** and **4**

Entry	Synthon	Imine[a]	Product	Isolated yield (%)[b]
1	**3**	PhCH=NPh		61
2	**3**	H_2C=NBn[c]		63
3	**3**	$(CH_2O)_n$ + $BnNH_2$		53
4	**3**	PhCH=NBn		74
5	**3**	PhCH=N-*t*Bu		44
6	**3**	PhCH=NMe		62
7	**4**	PhCH=NPh		76
8	**4**	H_2C=NBn[c]		41

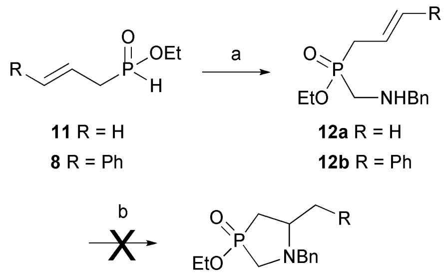
[a] Conditions: imine or triazine (1 equiv.), Cs_2CO_3 (1.5 equiv.), $Pd(PPh_3)_4$ (2 mol%), toluene, reflux, 24 h. [b] Yield of pure compound after column chromatography. [c] 1,3,5-tribenzylhexahydro-1,3,5-triazine was used.

aminomethylated iodide **9** in moderate isolated yield. Compound **9** was subjected to Heck-type[9] reaction conditions (Pd/dppf, 2 mol%) in DMF to produce the desired 7-membered ring heterocycle **10** in 35% isolated yield. We have not optimized this reaction, other than the use of dppf[10] instead of PPh_3. While more work would be required to fully explore this strategy, Scheme 5 provides an interesting "proof of concept", and the basis for future experiments.

Along similar lines, we briefly attempted the Wacker-type cyclization[11] of unsaturated amino-*H*-phosphinate **12** (Scheme 6). Unfortunately, attempts on **12a** and **12b** were unsuccessful. The use

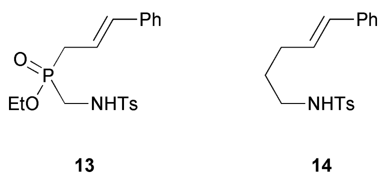


Scheme 5 Tandem aminomethylation–Heck cyclization. (a) $(EtO)_4Si$, toluene, reflux, 24 h, 92%; (b) 2-iodoaniline (1.2 equiv.), paraformaldehyde (1.2 equiv.), toluene, reflux, 16 h, 46%; (c) $Pd(OAc)_2$ (2 mol%), dppf (2.2 mol%), *i*-Pr_2NEt (2 equiv.), DMF, 110 °C, 35%.



Scheme 6 Attempted Pd(II)-catalyzed cyclization. (a) 1,3,5-tribenzylhexahydro-1,3,5-triazine (0.4 equiv.), toluene, reflux, 16 h, **12a** 57%; **12b** 83%. (b) $Pd(OAc)_2$ (5 mol%), AcONa (2 equiv.), DMSO, O_2, 80 °C, 60 h.

of ethyl cinnamyl-*H*-phosphinate **8** *via* sulfonamide **13** similarly failed, although Liu and Stahl reported the successful cyclization of the all-carbon analog **14**.[11c]



13 **14**

Admittedly, we have not fully investigated the palladium-catalyzed heterocyclizations of precursors **9**, **12** and **13**. In spite of the above failed experiments, tremendous flexibility remains available to synthesize phosphorus heterocycles from simple precursors. For example, Wolfe-type carboaminations[12] could also be tried on aminophosphinate precursors **12** and **13**. Similarly, the use of allyl amine in the place of 2-iodoaniline (Scheme 5) could lead to a ring-closing metathesis precursor (the reaction of **8** with paraformaldehyde and allyl amine gives the corresponding diene in 53% yield). Our methodologies have made available a wide range of compounds through hydrophosphinylation, cross-coupling (halides, carboxylates, alcohols), alkylation, *etc.*,[3] so that novel P-containing precursors could lead to facile syntheses of heterocyclic products. The preparation of P,O-heterocycles through the well-known addition of *H*-phosphinates to carbonyl compounds, using the precursors described in the present work, was not investigated because P,N-heterocycles are likely to be more interesting as amino acid analogs.[13]

Conclusions

The facile synthesis of P,N-heterocycles (substituted 3-hydroxy-1,3-azaphospholane and 3-hydroxy-1,3-azaphosphorinane-3-oxides) is described. With aryl bromide precursors, the cyclization proceeded well using $Pd(PPh_3)_4$ (2 mol%) as the cross-coupling catalyst. The availability of simple *H*-phosphinate building blocks opens up the possibility for the synthesis of various phosphorus heterocycles. Catalytic methods for the cyclization of other phosphinate precursors for the preparation of P,N- as well as other P-heterocycles will be the object of future studies.

Experimental

For general chemistry information, and additional details on the synthesis of precursors and intermediates, spectral data, and a copy of the ^{31}P, ^{1}H and ^{13}C NMR spectra, see the ESI.†

Ethyl (3-chloropropyl)-*H*-phosphinate (Scheme 2, compound 1)

To (3-chloropropyl)-*H*-phosphinic acid[3g] (2.56 g, 18 mmol) in toluene (60 mL) was added tetraethyl orthosilicate (1.5 equiv., 5.63 g) under N_2, and the mixture was refluxed for 24 h. The solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (silica, EtOAc 100%) to afford the desired product as a yellow oil (1.22 g, 40%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (d, J = 533 Hz, 1H, H–P), 4.00-4.30 (m, 2H, $–CH_2–O–$), 3.64 (t, J = 5 Hz, 2H, $–CH_2–Cl$), 1.85-2.10 (m, 4H, 2 x $–CH_2–$), 1.39 (t, J = 7 Hz, 3H, $CH_3–$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.8 (d, J_{POC} = 6 Hz), 44.9 (d, J_{PCCCCl} = 17 Hz), 26.3 (d, J_{PC} = 95 Hz), 24.2 (d, J_{PCC} = 2 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.7 (d, J = 533 Hz); HRMS (EI^+) calc. for $C_5H_{12}ClO_2P$ 171.0342, found 171.0346.

Ethyl (3-bromobutyl)-*H*-phosphinate (eqn (2), compound 2)[3e]

To a solution of $EtOP(O)H_2$ in CH_3CN (2 equiv., 60 mmol, 120 mL) and 4-bromo-1-butene (30 mmol, 4.05 g, 3 mL) were added Pd_2dba_3 (0.5 mol%, 137 mg) and xantphos (1.1 mol%, 191 mg). After 16 h of reflux, the mixture was concentrated and the resulting oil was diluted in EtOAc (60 mL) and washed with brine (1 × 20 mL). The organic layer was dried and concentrated. The resulting oil was purified by column chromatography (silica, EtOAc 100%) to afford the desired product as a yellow oil (4.6 g, 67%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, J = 530 Hz, 1H, H–P), 4.00-4.35 (m, 2H, $–CH_2–O$), 3.43 (t, J = 7 Hz, 2H, $–CH_2–Br$), 1.95-2.10 (m, 2H, $–CH_2–$), 1.65-1.90 (m, 4H, 2 x $–CH_2–$), 1.37 (t, J = 7 Hz, 3H, $CH_3–$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 62.6 (d, J_{POC} = 7 Hz), 33.1 (d, J_{PCC} = 15 Hz), 32.7, 27.9 (d, J_{PC} = 94 Hz), 19.6, 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 38.8 (d, J = 530 Hz); HRMS (EI^+) calc. for $C_6H_{14}BrO_2P$ 228.9993, found 228.9990.

Ethyl 2-(2-bromophenyl)ethyl-*H*-phosphinate (eqn (3), compound 5)

To a solution of $EtOP(O)H_2$ in CH_3CN (1.6 equiv., 32 mmol, 64 mL) and 2-bromostyrene (20 mmol, 3.66 g) were added Pd_2dba_3 (0.75 mol%, 137 mg) and xantphos (1.6 mol%, 185 mg). After 16 h of reflux, the mixture was concentrated and the resulting oil was diluted in EtOAc (30 mL) and washed with brine (1 × 10 mL). The organic layer was dried and concentrated. The resulting oil was purified by column chromatography (silica, EtOAc–hexanes 7 : 3, v/v) to afford the desired product as a yellow oil (3.56 g, 64%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, J = 8 Hz, 1H, *aro* CH), 7.20-7.35 (m, 2H, *aro* CH), 7.14 (d, J = 532 Hz, 1H, H–P), 7.00-7.15 (m, 1H, *aro* CH), 4.00-4.25 (m, 2H, $–CH_2–O–$), 2.90-3.10 (m, 2H, $–CH_2–P$), 2.00-2.20 (m, 2H, $–C–CH_2–$), 1.37 (t, J = 14, 7 Hz, 3H, $CH_3–$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 139.6 (d, J_{PCCC} = 16 Hz), 133.2, 130.5, 128.6, 127.9, 124.3, 62.7 (d, J_{POC} = 7 Hz), 28.9 (d, J_{PC} = 92 Hz), 27.9, 16.5 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 37.4 (d, J = 532 Hz).

Ethyl (2-bromobenzyl)-*H*-phosphinate (Scheme 4, compound 4)

To ethyl (1,1-diethoxyethyl)-(2-bromobenzyl)phosphinate (3.03 g, 8 mmol) in 20 mL of 10% ethanol in dichloromethane was added chlorotrimethylsilane (1.5 equiv., 12 mmol, 1.3 mL) under N_2 and the clear solution was stirred for 16 h at room temperature.[6] The solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (silica, EtOAc–hexanes 3 : 7, v/v) to afford the desired product as a yellow oil (2.1 g, 99%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, J = 8 Hz, 1H, *aro* CH), 7.20-7.40 (m, 2H, *aro* CH), 7.10-7.20 (m, 1H, *aro* CH), 7.16 (d, J = 544 Hz, 1H, H–P), 4.00-4.25 (m, 2H, $–CH_2–O–$), 3.35-3.55 (m, 2H, $C–CH_2–P$), 1.32 (t, J = 14, 7 Hz, 3H, $CH_3–$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 133.2 (d, J = 2 Hz), 132.1 (d, J = 6 Hz), 130.7 (d, J = 7 Hz), 129.2 (d, J = 4 Hz), 128.1 (d, J = 4 Hz), 124.8 (d, J = 7 Hz), 63.0 (d, J_{POC} = 6 Hz), 37.3 (d, J_{PC} = 89 Hz), 16.4 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 34.3 (d, J = 544 Hz); HRMS (EI^+) calc. for $C_9H_{12}BrO_2P$ 262.9837, found 262.9835.

General procedure for the cyclization from compound 1 or 2

To the compound **1** or **2** (1 mmol) in toluene (10 mL) was added *N*-benzylideneaniline (1.2 equiv.) or 1,3,5-tribenzylhexahydro-1,3,5-triazine (0.4 equiv) and the mixture was refluxed for 16 h. The solvent was removed *in vacuo*, and the resulting oil was diluted in EtOAc (30 mL) and washed with brine (1 × 10 mL). The organic layer was dried and concentrated. The resulting oil was purified by column chromatography (silica, EtOAc–hexanes 3 : 7, v/v) to afford the desired product.

1,2-Diphenyl-3-ethoxy-1,3-azaphosphorinane-3-oxide (Table 1, entry 1). Yellow oil, yield: 61%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00-7.50 (m, 7H, *aro* CH), 6.50-6.80 (m, 3H, *aro* CH), 4.80-5.00 (m, 1H, $–CH_2–$), 4.55-4.75 (m, 1H, –P–CH–N–), 4.00-4.25 (m, 2H, $–CH_2–O–)_a$, 3.20-3.40 and 3.65-3.85 (m, 2H, $–CH_2–O–)_b$, 3.55-3.60 (m, 1H, $–CH_2–$), 3.40-3.50 (m, 1H, $–CH_2–$), 2.00-2.20 (m, 1H, $–CH_2–$), 1.60-2.00 (m, 2H, $–CH_2–$), 1.20-1.40 (m, 3H, $CH_3–)_a$, 1.03 (t, J = 14, 7 Hz, 3H, $CH_3–)_b$; ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 146.4, 146.2, 135.9, 135.5, 129.5, 129.2, 128.9, 128.3, 128.2 (d, J = 4 Hz), 127.8 (d, J = 4 Hz), 118.8, 114.3 (d, J = 6 Hz), 62.4 (d, J_{POC} = 7 Hz)$_a$, 62.1 (d, J_{POC} = 7 Hz)$_b$, 57.9 (d, J_{PC} = 93 Hz)$_b$, 57.7 (d, J_{PC} = 96 Hz)$_a$, 45.4 (d, J_{PCC} = 5 Hz)$_a$, 45.1 (d, J_{PCC} = 6 Hz)$_b$, 25.4 (d, J_{PC} = 92 Hz)$_a$, 25.2, 24.3 (d, J_{PC} = 95 Hz)$_b$, 16.9 (d, J_{POCC} = 5 Hz)$_a$, 16.6 (d, J_{POCC} = 6 Hz)$_b$; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 50.6 (s), 51.6 (s); HRMS (EI^+) calc for $C_{18}H_{22}NO_2P$ 315.1388, found 315.1388.

1-Benzyl-3-ethoxy-1,3-azaphosphorinane-3-oxide (Table 1, entry 2). Yellow oil, yield: 58%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.35 (m, 5H, *aro* CH), 3.90-4.20 (m, 2H, $-CH_2-O-$), 3.71 (dd, J = 12, 2 Hz, 1H, $-CH_2-$), 3.49 (dd, J = 13, 2 Hz, 1H, $-CH_2-$), 2.96 (t, J = 15 Hz, 1H, $-CH_2-$), 2.79 (d, J = 12 Hz, 1H, $-CH_2-$), 2.45 (d, J = 15 Hz, 1H, $-CH_2-$), 2.20-2.35 (m, 1H, $-CH_2-$), 1.85-2.10 (m, 3H, $-CH_2-CH_2-$), 1.60-1.80 (m, 1H, $-CH_2-$), 1.33 (t, J = 14, 7 Hz, 3H, CH_3-); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 137.4, 129.2 (2C), 128.5 (2C), 127.6, 64.4 (d, J_{PCNC} = 15 Hz), 60.4 (d, J_{POC} = 7 Hz), 54.2 (d, J_{PCCC} = 5 Hz), 52.2 (d, J_{PC} = 98 Hz), 25.6 (d, J_{PC} = 89 Hz), 23.4 (d, J_{PCC} = 6 Hz), 16.7 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 44.2 (s); HRMS (EI$^+$) calc. for $C_{13}H_{20}NO_2P$ 253.1232, found 253.1230.

1,2-Diphenyl-3-ethoxy-1,3-azaphosphepane-3-oxide (Table 1, entry 3). Yellow oil, yield: 76%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.50-7.60 (m, 10H, *aro* CH), 4.69 (d, J = 17 Hz, 1H, $-P-CH-N-)_a$, 4.61 (d, J = 16 Hz, 1H, $-P-CH-N-)_b$, 3.70-3.85 and 4.00-4.30 (m, 2H, $-CH_2-O-$), 3.39 (t, J = 13, 6 Hz, 1H, $-CH_2-$), 3.29 (t, J = 13, 7 Hz, 1H, $-CH_2-$), 1.70-2.00 (m, 4H, $-CH_2-CH_2-$), 1.50-1.65 (m, 2H, $-CH_2-$), 1.28 (t, J = 14, 7 Hz, 3H, $-CH_3-)_a$, 1.02 (t, J = 14, 7 Hz, 3H, $-CH_3-)_b$; ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 146.3, 136.1, 135.6, 133.2, 132.1, 129.4, 129.1 (d, J = 2 Hz), 128.9 (d, J = 2 Hz), 128.3 (d, J = 4 Hz)$_a$, 127.8 (d, J = 4 Hz)$_b$, 118.9, 114.4, 111.8, 62.3 (d, J_{POC} = 7 Hz)$_a$, 61.9 (d, J_{POC} = 7 Hz)$_b$, 57.9 (d, J_{PC} = 91 Hz)$_a$, 57.6 (d, J_{PC} = 95 Hz)$_b$, 33.6 (d, J_{PCC} = 3 Hz)$_a$, 33.4 (d, J_{PCC} = 3 Hz)$_b$, 33.0, 32.9, 26.9 (d, J_{PC} = 78 Hz)$_a$, 25.7 (d, J_{PC} = 80 Hz)$_b$, 20.7 (d, J_{PCCC} = 5 Hz)$_a$, 20.3 (d, J_{PCCC} = 4 Hz)$_b$, 16.9 (d, J_{POCC} = 5 Hz)$_a$, 16.7 (d, J_{POCC} = 5 Hz)$_b$; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 51.8 (s), 50.9 (s); HRMS (EI$^+$) calc. for $C_{19}H_{24}NO_2P$ 329.1544, found 329.1545.

1-Benzyl-3-ethoxy-1,3-azaphosphepane-3-oxide (Table 1, entry 4). Yellow oil, yield: 45%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.35 (m, 5H, *aro* CH), 3.90-4.00 (m, 1H, $-N-CH_2-P$), 3.60-3.80 (m, 3H, $-N-CH_2-P$ and $-CH_2-O$), 2.90-3.10 (m, 2H, $-N-CH_2-P$), 2.80-2.90 (m, 1H, $-CH_2-$), 2.60-2.70 (m, 1H, $-CH_2-$), 2.00-2.20 (m, 3H, $-CH_2-CH_2-$), 1.55-1.90 (m, 3H, $-CH_2-CH_2-$), 1.23 (t, J = 14, 7 Hz, 3H, $-CH_3-$); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 138.7, 129.2 (2C), 128.5 (2C), 127.5, 64.2 (d, J_{PCNC} = 16 Hz), 60.0 (d, J_{POC} = 7 Hz), 58.3, 54.5 (d, J_{PCC} = 105 Hz), 30.2, 29.1 (d, J_{PC} = 88 Hz), 19.9 (d, J_{PCC} = 2 Hz), 16.7 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 63.1 (s); HRMS (EI$^+$) calc. for $C_{14}H_{22}NO_2P$ 267.1388, found 267.1389.

General procedure for the cyclization from compound 3 or 4

To compound **3** or **4** (5 mmol) in toluene (50 mL) was added the corresponding imine (1.2 equiv.) and the mixture was refluxed for 16 h. Then, caesium carbonate (1.2 equiv.) and $Pd(PPh_3)_4$ (2 mol%) were added, and the mixture was refluxed for 24 h. The solvent was removed *in vacuo*, and the resulting oil was diluted in EtOAc (30 mL) and washed with brine (1 × 10 mL). The organic layer was dried and concentrated. The resulting oil was purified by column chromatography (silica, EtOAc–hexanes 3 : 7, v/v) to afford the desired product.

1,2-Diphenyl-3-ethoxy-1,2-dihydro-benzo[1,3]azaphosphole-3-oxide (Table 2, entry 1). Yellow oil, yield: 61%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.80-7.70 (m, 14H, *aro* CH), 5.13 (d, J = 15 Hz, 1H, $-N-CH-P-)_b$, 4.79 (d, J = 17 Hz, 1H, $-N-CH-P-)_a$, 4.20-4.30 (m, 2H, $-CH_2-O-)_a$, 3.85-3.95 and 3.20-3.30 (m, 2H, $-CH_2-O-)_b$, 1.38 (t, J = 14, 7 Hz, 3H, $CH_3-)_a$, 0.95 (t, J = 14 Hz, 3H, $CH_3-)_b$; ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 154.7 (d, J = 22 Hz)$_b$, 152.9 (d, J = 22 Hz)$_a$, 143.2 (d, J = 8 Hz)$_a$, 142.3 (d, J = 10 Hz)$_b$, 134.8 (d, J = 2 Hz)$_b$, 134.6 (d, J = 2 Hz)$_a$, 134.1 (d, J = 7 Hz), 129.8, 129.7, 129.5 (d, J = 6 Hz), 129.1 (d, J = 2 Hz), 128.9 (d, J = 6 Hz), 128.8 (d, J = 2 Hz), 128.2 (d, J = 3 Hz), 128.18, 128.12, 127.6 (d, J = 5 Hz), 126.1, 125.6 (d, J = 83 Hz), 123.2, 120.3, 120.1, 119.9, 112.8 (d, J = 10 Hz)$_a$, 112.1 (d, J = 11 Hz)$_b$, 65.6 (d, J_{PC} = 96 Hz)$_b$, 64.8 (d, J_{PC} = 99 Hz)$_a$, 62.6 (d, J_{POC} = 7 Hz)$_b$, 62.1 (d, J_{POC} = 7 Hz)$_a$, 16.9 (d, J_{POCC} = 6 Hz)$_a$, 16.4 (d, J_{POCC} = 6 Hz)$_b$; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 50.6 (s), 49.4 (s); HRMS (EI$^+$) calc. for $C_{21}H_{20}NO_2P$ 349.1232, found 349.1237.

1-Benzyl-3-ethoxy-1,2-dihydro-benzo[1,3]azaphosphole-3-oxide (Table 2, entry 2). Yellow oil, yield: 63%: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20-7.80 (m, 7H, *aro* CH), 6.75-6.85 (m, 2H, *aro* CH), 4.52 (q, J = 16 Hz, 2H, $-N-CH_2-P-$), 4.10-4.20 (m, 2H, $-CH_2-O-$), 3.37 (dd, J = 13, 5 Hz, 2H, $-N-CH_2-Ph$), 1.34 (t, J = 14, 7 Hz, 3H, CH_3-); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.3 (d, J = 23 Hz), 136.8, 135.0 (d, J = 2 Hz), 132.3 (d, J = 16 Hz), 129.1, 128.8, 128.7 (d, J = 5 Hz), 127.9, 127.4, 117.9 (d, J = 12 Hz), 113.2 (d, J = 131 Hz), 109.9 (d, J = 12 Hz), 61.9 (d, J_{POC} = 6 Hz), 52.5 (d, J_{PCNC} = 6 Hz), 47.6 (d, J_{PC} = 102 Hz), 16.8 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 52.4 (s); HRMS (EI$^+$) calc. for $C_{16}H_{18}NO_2P$ 287.1075, found 287.1080.

1-Benzyl-3-ethoxy-2-phenyl-1,2-dihydro-benzo[1,3]azaphosphole-3-oxide (Table 2, entry 4). Yellow oil, yield: 74%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.65-7.70 (m, 14H, *aro* CH), 4.75 (d, J = 16 Hz, 2H, $-N-CH-Ph$), 4.61 (d, J = 14 Hz, 1H, $-N-CH-P-)_b$, 4.41 (d, J = 16 Hz, 1H, $-N-CH_2-P-)_a$, 4.00-4.25 (m, 2H, $-CH_2-O-)_a$, 3.15-3.35 and 3.75-3.95 (m, 2H, $-CH_2-O-)_b$, 1.32 (t, J = 14, 7 Hz, 3H, $CH_3-)_a$, 0.91 (t, J = 14 Hz, 3H, $CH_3-)_b$; ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 155.2 (d, J = 23 Hz)$_b$, 154.6 (d, J = 23 Hz)$_a$, 137.0, 136.4, 135.21, 135.18, 133.87, 133.82, 133.74, 132.3 (d, J = 10 Hz), 129.5 (d, J = 5 Hz), 129.2 (d, J = 2 Hz)$_a$, 129.1 (d, J = 2 Hz)$_b$, 129.0, 128.5 (d, J = 2 Hz), 128.3 (d, J = 4 Hz), 127.73, 127.69, 127.63, 127.3, 118.7 (d, J = 12 Hz)$_b$, 118.2 (d, J = 12 Hz)$_a$, 113.5, 113.1, 111.7, 111.4, 110.7 (d, J = 11 Hz)$_a$, 109.4 (d, J = 11 Hz)$_b$, 63.4 (d, J_{PC} = 98 Hz)$_b$, 62.5 (d, J_{POC} = 7 Hz)$_b$, 61.95 (d, J_{PC} = 101 Hz)$_a$, 61.93 (d, J_{POC} = 7 Hz)$_a$, 49.1 (d, J_{PCNC} = 8 Hz)$_b$, 48.9 (d, J_{PCNC} = 8 Hz)$_a$, 17.0 (d, J_{POCC} = 6 Hz)$_a$, 16.4 (d, J_{POCC} = 6 Hz)$_b$; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 51.1 (s), 49.8 (s); HRMS (EI$^+$) calc. for $C_{22}H_{22}NO_2P$ 363.1388, found 363.1395.

1-*tert*-Butyl-3-ethoxy-2-phenyl-1,2-dihydro-benzo[1,3]azaphosphole-3-oxide (Table 2, entry 5). Yellow oil, yield: 44%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.70-7.80 (m, 9H, *aro* CH), 4.84 (d, J = 20 Hz, 1H, $-N-CH-P-)_b$, 4.66 (d, J = 20 Hz, 1H, $-N-CH-P-)_a$, 4.00-4.25 (m, 2H, $-CH_2-O-)_a$, 3.15-3.35 and 3.75-3.95 (m, 2H, $-CH_2-O-)_b$, 1.43 (s, 9H, $-N-C(CH_3)_3)_a$, 1.41 (s, 9H, $-N-C(CH_3)_3)_b$, 1.33 (t, J = 14, 7 Hz, 3H, $CH_3-)_a$, 0.80 (t, J = 14 Hz, 3H, $CH_3-)_b$; ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 154.7 (d, J = 25 Hz)$_b$, 154.1 (d, J = 24 Hz)$_a$, 139.1 (d, J = 4 Hz), 137.1, 134.18, 134.15, 134.13, 132.3 (d, J = 10 Hz), 130.1 (d, J = 6 Hz)$_a$, 129.3 (d, J = 5 Hz)$_b$, 129.04, 129.01, 128.97, 127.8 (d, J = 3 Hz)$_a$, 127.6 (d, J = 3 Hz)$_b$, 126.9 (d, J = 4 Hz)$_a$, 126.8 (d, J = 4 Hz)$_b$, 118.1 (d, J = 12 Hz)$_b$, 117.7 (d, J = 12 Hz)$_a$, 115.5, 114.8 (d, J = 11 Hz)$_b$, 114.1 (d, J = 10 Hz)$_b$, 113.8, 62.7 (d, J_{POC} = 7 Hz)$_b$, 61.9 (d, J_{PC} = 93 Hz)$_b$, 61.6 (d,

J_{POC} = 7 Hz)$_a$, 60.3 (d, J_{PC} = 100 Hz)$_a$, 57.7 (d, J_{PCNC} = 6 Hz)$_b$, 56.8 (d, J_{PCNC} = 6 Hz)$_a$, 29.6 (3C)$_b$, 29.5 (3C)$_a$,16.9 (d, J_{POCC} = 6 Hz)$_a$, 16.2 (d, J_{POCC} = 6 Hz)$_b$; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 52.3 (s), 51.3 (s); HRMS (EI$^+$) calc. for $C_{19}H_{24}NO_2P$ 329.1545, found 329.1546.

3-Ethoxy-1-methyl-2-phenyl-1,2-dihydro-benzo[1,3]azaphosphole-3-oxide (Table 2, entry 6). White solid mp 114–116 °C, yield: 62%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.70-7.70 (m, 9H, *aro* CH), 4.45 (d, J = 15 Hz, 1H, –N–CH–P–)$_b$, 4.32 (d, J = 15 Hz, 1H, –N–CH–P–)$_a$, 4.15-4.25 (m, 2H, –CH_2–O–)$_a$, 3.10-3.30 and 3.75-3.95 (m, 2H, –CH_2–O–)$_b$, 2.84 (s, 3H, –N–CH_3)$_b$, 2.83 (s, 3H, –N–CH_3)$_a$, 1.37 (t, J = 14, 7 Hz, 3H, CH_3–)$_a$, 0.89 (t, J = 14 Hz, 3H, CH_3–)$_b$; ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 156.2 (d, J = 23 Hz)$_a$, 155.4 (d, J = 23 Hz)$_b$, 135.17, 135.15, 135.12, 135.09, 134.0 (d, J = 7 Hz), 133.9 (d, J = 4 Hz), 129.19, 129.17, 129.10, 129.07, 128.8 (d, J = 5 Hz), 128.47, 128.43, 128.39, 128.1 (d, J = 5 Hz), 127.8 (d, J = 4 Hz), 118.8 (d, J = 12 Hz)$_b$, 117.9 (d, J = 12 Hz)$_a$, 113.3 (d, J = 20 Hz), 111.7 (d, J = 17 Hz), 110.3 (d, J = 11 Hz)$_b$, 109.1 (d, J = 11 Hz)$_a$, 66.5 (d, J_{PC} = 98 Hz)$_b$, 64.8 (d, J_{PC} = 101 Hz)$_a$, 62.4 (d, J_{POC} = 7 Hz)$_a$, 61.9 (d, J_{POC} = 7 Hz)$_b$, 34.2 (d, J_{PCNC} = 11 Hz)$_a$, 33.5 (d, J_{PCNC} = 10 Hz)$_b$, 16.9 (d, J_{POCC} = 6 Hz)$_a$, 16.4 (d, J_{POCC} = 6 Hz)$_b$; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 50.5 (s), 49.1 (s); HRMS (EI$^+$) calc. for $C_{16}H_{18}NO_2P$ 287.1075, found 287.1073.

1,2-Diphenyl-3-ethoxy-1,2,3,4-tetrahydro-benzo[*d*][1,3]azaphosphinine (Table 2, entry 7). Yellow oil, yield: 76%: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.80-7.60 (m, 14H, *aro* CH), 5.26 (d, J = 22 Hz, 1H, –N–CH–P–)$_b$, 5.06 (d, J = 25 Hz, 1H, –N–CH–P–)$_a$, 4.10-4.30 (m, 2H, –CH_2–O–)$_a$, 3.95-4.10 (m, 1H, –CH_2–O–)$_b$, 3.60-3.75 (m, 1H, -CH_2–O–)$_b$, 3.00-3.30 (m, 2H, –C–CH_2–P–), 1.28 (t, J = 14, 7 Hz, 3H, CH_3-)$_a$, 0.76 (t, J = 14, 7 Hz, 1H, CH_3–)$_b$; ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 149.2 (d, J = 4 Hz)$_a$, 148.5 (d, J = 4 Hz)$_b$, 143.2 (d, J = 9 Hz)$_a$, 142.8 (d, J = 9 Hz)$_b$, 138.4, 136.6 (d, J = 6 Hz), 132.3 (d, J = 12 Hz)$_a$, 130.9 (d, J = 7 Hz)$_b$, 129.7, 129.2, 129.17, 129.15, 128.9 (d, J = 2 Hz), 128.5 (d, J = 2 Hz), 128.2, 127.87, 127.84, 127.3 (d, J = 4 Hz), 126.8 (d, J = 4 Hz), 126.6 (d, J = 10 Hz), 125.7 (d, J = 2 Hz), 125.1, 123.9, 122.2 (d, J = 9 Hz)$_a$, 121.9, 121.6 (d, J = 7 Hz)$_b$, 120.9, 117.3, 63.2 (d, J_{PC} = 95 Hz)$_b$, 62.8 (d, J_{PC} = 91 Hz)$_a$, 61.7 (d, J_{POC} = 7 Hz)$_b$, 61.6 (d, J_{POC} = 7 Hz)$_a$, 31.5 (d, J_{PC} = 84 Hz)$_b$, 28.6 (d, J_{PC} = 86 Hz)$_a$, 16.7 (d, J_{POCC} = 6 Hz)$_a$, 16.4 (d, J_{POCC} = 6 Hz)$_b$; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 43.0 (s), 54.4 (s); HRMS (EI$^+$) calc. for $C_{22}H_{22}NO_2P$ 363.1388, found 363.1382.

1-Benzyl-3-ethoxy-1,2,3,4-tetrahydro-benzo[*d*][1,3]azaphosphinine (Table 2, entry 8). Yellow oil, yield: 41%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10-7.80 (m, 7H, *aro* CH), 6.80-7.00 (m, 2H, *aro* CH), 4.35 (dd, J = 5, 2 Hz, 2H, –N–CH_2–P–), 3.85-4.20 (m, 2H, –CH_2–O–), 3.05-3.25 (m, 4H, –C–CH_2–P– and –N–CH_2–Ph), 1.24 (t, J = 14, 7 Hz, 3H, CH_3–); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 148.3 (d, J = 4 Hz), 137.3, 132.3 (d, J = 10 Hz), 132.2, 131.0 (d, J = 10 Hz), 128.76 (d, J = 12 Hz), 128.72 (d, J = 35 Hz), 128.4 (d, J = 2 Hz), 127.9, 123.0 (d, J = 7 Hz), 122.9, 115.9 (d, J = 2 Hz), 61.0 (d, J_{POC} = 7 Hz), 57.2 (d, J_{PCNC} = 12 Hz), 48.3 (d, J_{PC} = 111 Hz), 31.6 (d, J_{PC} = 87 Hz), 16.7 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 57.2 (s); HRMS (EI$^+$) calc. for $C_{17}H_{20}NO_2P$ 301.1232, found 301.1227.

Formation *in situ* of the imine from an aldehyde (Table 2, entry 3)

To the compound **3** (5 mmol) in toluene (50 mL) were added benzylamine (1.2 equiv., 0.65 mL) and paraformaldehyde (1.2 equiv., 198 mg), and the mixture was refluxed for 16 h. Then, caesium carbonate (1.2 equiv.) and $Pd(PPh_3)_4$ (2 mol%) were added and the mixture was refluxed for 24 h. The solvent was removed *in vacuo*, and the resulting oil was diluted in EtOAc (30 mL) and washed with brine (1 × 10 mL). The organic layer was dried and concentrated. The resulting oil was purified by column chromatography (silica, EtOAc–hexanes 3 : 7, v/v) to afford the desired product as a yellow oil (760 mg, 53%).

Heck product (Scheme 5, compound 10)

To compound **9** (0.5 mmol, 221 mg) in DMF (2.5 mL) was added *N*,*N*-diisopropylethylamine (2 equiv., 1 mmol, 0.2 mL), 1,1′-bis(diphenylphosphino)ferrocene (2.2 mol%, 6.1 mg) and $Pd(OAc)_2$ (2 mol%, 2.2 mg). After 40 h of reflux, the solvent was removed *in vacuo*, and the resulting oil was diluted in EtOAc (10 mL) and washed with brine (1 × 20 mL). The organic layer was dried and concentrated. The resulting oil was purified by column chromatography (silica, EtOAc 100%) to afford the desired product as a pink oil (54.7 mg, 35%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20-7.60 (m, 6H, *aro* CH), 7.13 (t, J = 15, 7 Hz, 1H, *aro* CH), 6.94 (d, J = 5 Hz, 1H, *aro* CH), 6.85 (t, J = 14, 7 Hz, 1H, *aro* CH), 6.67 (d, J = 8 Hz, 1H, –C=CH–Ph), 4.00-4.25 (m, 1H, –NH–), 3.90-4.00 (m, 1H, –CH_2–O–), 3.45-3.70 (m, 3H, P–CH_2–N– and P–CH_2–C–), 3.35-3.45 (m, 1H, –CH_2–O–), 3.15-3.25 (m, 1H, P–CH_2–C–), 1.09 (t, J = 14, 7 Hz, 3H, CH_3–); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 145.5 (d, J = 2 Hz), 137.5 (d, J = 3 Hz), 133.0 (d, J = 7 Hz), 131.9 (d, J = 11 Hz), 131.56, 131.54, 129.6, 128.9 (d, J = 2 Hz), 128.88, 128.81, 128.5 (d, J = 2 Hz), 127.3, 119.9, 118.3, 60.9 (d, J_{POC} = 7 Hz), 44.3 (d, J_{PC} = 119 Hz), 31.4 (d, J_{PC} = 78 Hz), 16.6 (d, J_{POCC} = 6 Hz); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 54.2 (s); HRMS (EI$^+$) calc. for $C_{18}H_{20}NO_2P$ 313.1232, found 313.1230.

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Notes and references

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