



Synthesis of new β - and γ -aminopyrrolidinephosphonates via 1,3-dipolar cycloaddition of substituted vinylphosphonates

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ABSTRACT

Synthesis of α - and β -(aminomethyl)vinylphosphonates was achieved from vinyl bromide via a cross-coupling reaction with triethyl phosphite and by cross-metathesis of allyl bromide and vinylphosphonate, respectively. The 1,3-dipolar cycloaddition of these vinylphosphonates with a dipole in the presence of trifluoroacetic acid afforded selectively the β -aminopyrrolidinephosphonates. Syntheses of *cis*- and *trans*- γ -aminopyrrolidinephosphonates are also described.

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1. Introduction

Vinylphosphonates have been known for several decades¹ and constitute a very important class of building blocks for the synthesis of complex structures,² including biologically active molecules.³ The β -aminovinylphosphonates, although rarely described,⁴ have been used for the synthesis of β -aminophosphonic acid derivatives⁵ that display interesting biological properties such as antibiotics,⁶ enzyme inhibitors,⁷ and anti-HIV agents.⁸ However, synthesis of heterocyclic β -aminophosphonates, in particular pyrrolidine analogues, remains a challenge.

Syntheses of substituted pyrrolidines are largely reported by cycloaddition of a 1,3-dipole with vinyl derivatives.⁹ To the best of our knowledge, only one 1,3-dipolar cycloaddition reaction has been reported between a 1,3-dipole and an unsubstituted vinylphosphonate to provide a heterocyclopentylphosphonate.¹⁰ On the contrary, the 1,3-dipolar cycloaddition reaction with substituted vinylphosphonate is still unknown.

In continuation of our work on the development of new methodology for the synthesis of heterocyclic aminophosphonic acids,¹¹ and considering the importance of heterocyclic aminophosphonates in synthetic, agrochemical, and medicinal chemistry,¹² we decided to investigate the 1,3-dipolar cycloaddition of α - and β -substituted vinylphosphonates with azomethine ylides to access a range of pyrrolidines, for phosphonopeptide construction (Fig. 1).

In this Letter, we report the synthesis of the first members of a new class of β - and γ -aminophosphoryl pyrrolidines.

2. Results and discussion

Synthesis of β -aminovinylphosphonates **1** was achieved by the S_N2 displacement of the allylic bromide **2** by oxazolidinone or amide **3** in the presence of a base (Cs_2CO_3 or NaH). Then, vinyl bromide **4** was coupled with triethyl phosphite at 150 °C in the presence of a catalytic amount of nickel bromide.¹³ The resulting vinylphosphonates **1** were obtained in good yields (Scheme 1, Table 1).¹⁴

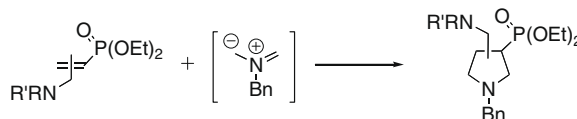
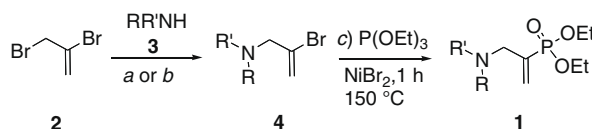


Figure 1. β - and γ -Aminopyrrolidinephosphonates.



Scheme 1. Synthesis of β -aminovinylphosphonates: see Table 1.

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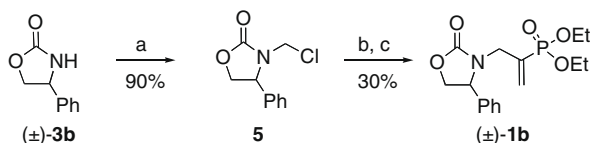
Table 1
Formation of vinylphosphonates **1a–c** produced via Scheme 1

Entry	R-NH-R' 3	4 (Yield %)	1^c (Yield %)	Vinylphosphonate 1a–c
1		4a (78) ^a	1a (74)	
2		4b (61) ^a	(±)- 1b (89)	
4		4c (76) ^b	1c (82)	

^a Reaction conditions: NaH, DMF, rt, 12 h.

^b Cs₂CO₃, CH₃CN, reflux, 2 h.

^c Solvent-free reaction of **4** with P(OEt)₃ 5 equiv, NiBr₂ 20 mol %, 150 °C, 1 h.



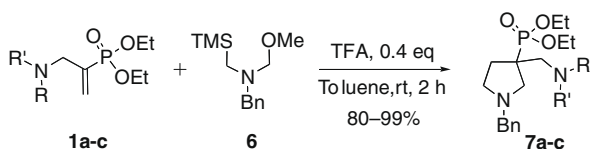
Scheme 2. Reagents and conditions: (a) (CH₂O)_n, TMSCl excess, reflux, 2 h; (b) NaH, CH₂[P(O)(OEt)₂]₂, THF, 0 °C; (c) NaH, (CH₂O)_n 5 equiv, THF, rt.

It is noteworthy that the preparation of **1b** from oxazolidinone (±)-**3b** by chloromethylation [(CH₂O)_n/TMSCl] to afford oxazolidinone **5**, and subsequent alkylation [CH₂[P(O)(OEt)₂]₂] and vinylation [NaH/(CH₂O)_n]^{4d} gave only a poor yield of the vinylphosphonate (±)-**1b** (Scheme 2).

For this study, the 1,3-dipole derived from **6** (an expensive commercial product) was prepared from benzylamine by following a well-known procedure.⁹ With vinylphosphonates **1a–c** in hand, we submitted them to a 1,3-dipolar cycloaddition with amine **6** in the presence of trifluoroacetic acid (TFA) in toluene at room temperature (Scheme 3). Under these conditions the desired β-aminophosphonates **7a–c** were produced in excellent yields (Table 2).¹⁵

In order to expand the scope of our method, we decided to prepare the heterocyclic aminophosphonates via the cycloaddition of dipole derived from **6** with the *cis*- and *trans*-γ-aminophosphonates **9c** and **12c**, respectively. The preparation of *cis*-vinylphosphonate **9c** was achieved by alkylation of *N*-tosyl amine **6c** followed by phosphorylation to provide aminoalkynephosphonate **8c**. Subsequent Lindlar hydrogenation (5 wt % Pd on CaCO₃) of the latter afforded the *cis*-γ-aminophosphonate **9c** in good yield.¹⁶

trans-Aminovinylphosphonate **12c** was prepared selectively by cross-metathesis of allyl amide **10** and vinylphosphonate **11** using Grubbs II catalyst (5 mol %)¹⁷ in dichloromethane at reflux for 20 h (Scheme 4).¹⁸ Assignment of the stereochemistry of **9c** and **12c** was confirmed by the analysis of ³J coupling constants between H-3 and the phosphorus atom. The observed values (³J_{PH_{trans}} = 51.7 Hz)

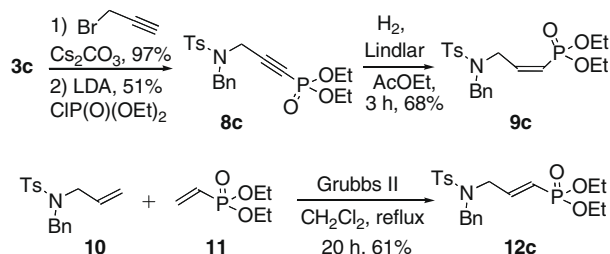


Scheme 3. β-Aminophosphonates by 1,3-dipolar cycloaddition.

Table 2
Formation of β-aminophosphonates **7a–c** produced via Scheme 3

Entry	R-NH-R' 1	7 (Yield %)	β-Aminophosphonates 7a–c
1	1a	7a (80)	
2	(±)- 1b	(±)- 7b (99) ^a	
4	1c	7c (91)	

^a Diastereoisomeric excess de = 8%.

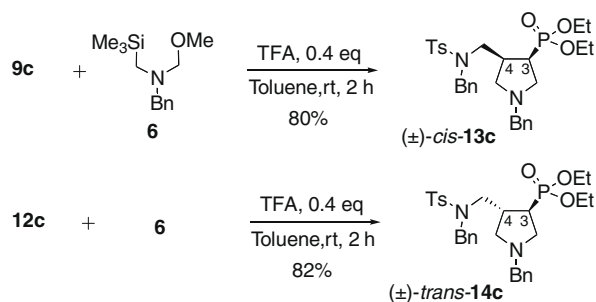


Scheme 4. Synthesis of γ-aminovinylphosphonates.

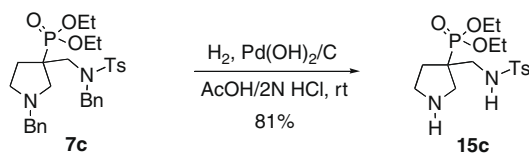
for **9c** and (³J_{PH_{cis}} = 22.0 Hz) for **12c** are in agreement with the literature.^{4c,d}

The 1,3-dipolar cycloaddition of *cis*- and *trans*-aminovinylphosphonates **9c** and **12c** was achieved under the same conditions as noted above. Amine **6** and aminovinylphosphonates **9c** and **12c** were treated with TFA in toluene at room temperature to produce, with complete stereoselectivity, the heterocyclic γ-aminophosphonates *cis*-**13c** and *trans*-**14c** in good yields (Scheme 5).¹⁹ The relative stereochemistry of *cis*-**13c** and *trans*-**14c** was supported by coupling constants in ¹³C NMR spectra between P and CH₂–C-4. The observed values (³J_{PC_{cis}} = 7.2 Hz) for **13c** and (³J_{PC_{trans}} = 0 Hz) for **14c** were in agreement with our reported data in a related system.²⁰

Selective deprotection of *N,N*-dibenzylaminophosphonate **7c** by hydrogenolysis with a catalytic amount of 20% Pd(OH)₂/C in AcOH/HCl under hydrogen (1 atm, 20 h), gave aminophosphonate **15c**²¹ in good yield (Scheme 6).²²



Scheme 5. Synthesis of *cis*- and *trans*-γ-aminophosphonates.



Scheme 6. Selective deprotection of amine by hydrogenolysis.

3. Conclusion

In summary, an easy and efficient synthesis of new β - and γ -aminopyrrolidinephosphonates involving a 1,3-dipolar cycloaddition of the corresponding vinyl phosphonates with a dipole in the presence of TFA has been described. Furthermore, new synthetic routes to vinylphosphonates have been developed via a cross-coupling reaction of vinyl bromide with triethyl phosphite to afford α -(amino-methyl)vinylphosphonates and via a cross-metathesis to provide a *trans*- β -(aminomethyl) analogue, in good yields. Further studies directed toward the asymmetric synthesis of β - and γ -aminopyrrolidinephosphonates are currently underway.

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- Data for **1a**: ^1H NMR (CDCl_3 , 360 MHz) δ = 1.27 (t, J = 7.0 Hz, 6H), 3.52 (dd, J = 8.5, 7.5 Hz, 2H, H-4'), 3.90–4.10 (m, 6H, 4H-6 and 2H-3), 4.27 (dd, J = 8.5, 7.3 Hz, 2H, H-5'), 5.88 (d, J_{PHtrans} = 45.8 Hz, 1H, H-1), 6.13 (d, J_{PHcis} = 22.0 Hz, 1H, H-1). ^{13}C NMR (CDCl_3 , 90.56 Hz) δ = 16.2 (d, J_{PC} = 6.2 Hz, CH_3), 16.4 (d, J_{PC} = 6.1 Hz, CH_3), 44.3 (C-4'), 45.8 (d, J_{PC} = 14.6 Hz, C-3), 61.8 (C-5'), 62.2 (d, J_{PC} = 5.9 Hz, CH_2OP), 131.4 (d, J_{PC} = 8.6 Hz, C-1), 134.5 (d, J_{PC} = 17.7 Hz, C-2), 158.1 (C-2'). ^{31}P NMR (CDCl_3 , 101.25 MHz) δ = 16.44. Data for **1b**: ^1H NMR (CDCl_3 , 360 MHz) δ = 1.25 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 3.41 (dd, J = 14.5, 15.4 Hz, 1H, H-3), 3.96–4.16 (m, 4H), 4.15 (dd, J = 6.1, 8.6 Hz, 1H, H-5'), 4.37 (dd, J = 9.0, 15.8 Hz, 1H, H-3), 4.63 (dd, J = 8.6, 9.0 Hz, 1H, H-5'), 4.85 (dd, J = 6.1, 9.0 Hz, 1H, H-4'), 5.77 (d, J_{PHtrans} = 45.7 Hz, 1H, H-1), 6.17 (d, J_{PHcis} = 21.6 Hz, 1H, H-1), 7.22–7.31 (m, 2H), 7.34–7.45 (m, 3H). ^{13}C NMR (CDCl_3 , 90.56 Hz) δ = 16.2 (d, J_{PC} = 2.6 Hz, CH_3), 16.3 (d, J_{PC} = 3.3 Hz, CH_2OP), 43.6 (d, J_{PC} = 13.9 Hz, C-3), 59.0 (C-4'), 62.2 (d, J_{PC} = 2.6 Hz, CH_2OP), 62.3 (d, J_{PC} = 2.6 Hz, CH_2OP), 69.9 (C-5'), [6 arom C: 127.1 (2CH), 129.1 (CH), 129.3 (2CH), 137.7 (Cq)], 132.4 (d, J_{PC} = 7.9 Hz, C-1), 133.9 (d, J_{PC} = 17.6 Hz, C-2), 157.8 (C-2'). ^{31}P NMR (CDCl_3 , 145.78 MHz) δ = 16.52. Data for **1c**: ^1H NMR (CDCl_3 , 250 MHz) δ = 1.27 (t, J = 7.0 Hz, 6H), 2.47 (s, 3H), 3.88–4.10 (m, 6H, 2CH₂O and 2H-3), 4.39 (s, 2H, benzyl), 5.93 (d, J_{PHtrans} = 46.8 Hz, 1H, H-1), 6.09 (d, J_{PHcis} = 22.7 Hz, 1H, H-1), 7.08–7.20 (m, 2H), 7.20–7.38 (m, 5H), 7.75 (d, J = 8.2 Hz, 2H). ^{13}C NMR (CDCl_3 , 62.9 Hz) δ = 16.2 (CH_3), 16.3 (CH_3), 21.6 (CH_3 , Ts), 47.7 (d, J_{PC} = 19.9 Hz, C-3), 51.8 (CH_2 benzyl), 62.0 (d, J_{PC} = 5.5 Hz, CH_2OP), [12 arom C: 127.3 (2CH), 128.0 (CH), 128.6 (2CH), 128.9 (2CH), 129.8 (2CH), 135.3 (Cq), 137.1 (Cq), 143.6 (Cq)], 130.6 (d, J_{PC} = 7.1 Hz, C-1), 130.6 (d, J_{PC} = 17.1 Hz, C-2). ^{31}P NMR (CDCl_3 , 101.25 MHz) δ = 17.00.
- Data for **7a**: ^1H NMR (CDCl_3 , 250 MHz) δ = 1.29 (t, J = 7.0 Hz, 6H, CH_3), 1.75–1.98 (m, 1H, H-4), 2.06–2.30 (m, 1H, H-4), 2.30–2.52 (m, 1H, H-5), 2.52–2.78 (m, 2H, CH_2N), 2.78–2.90 (m, 1H, H-5), 3.34–3.82 (m, 6H, 2H-2, 2H-4 and 2H_{benzyl}), 4.00–4.40 (m, 6H, 2H-5' and 4H, CH_2OP), 7.05–7.40 (m, 5H). ^{13}C NMR (CDCl_3 , 62.9 Hz) δ = 16.6 (2 CH_3), 30.7 (C-4), 45.3 (d, J_{PC} = 14.7 Hz, C-3), 46.5 (C-4'), 50.4 (C-2), 53.7 (d, J_{PC} = 3.6 Hz, C-5), 58.6 (CH_2N), 59.6 (CH_2 benzyl), 61.9 (C-5'), 62.2 (d, J_{PC} = 7.4 Hz, CH_2OP), 62.5 (d, J_{PC} = 7.0 Hz, CH_2OP), [6 arom C: 127.0 (CH), 128.2 (2CH), 128.6 (2CH), 138.8 (Cq)], 159.6 (C-2'). ^{31}P NMR (CDCl_3 , 101.25 MHz) δ = 31.77. Data for **7b**: ^1H NMR (CDCl_3 , 250 MHz) two diastereoisomers (a/b, 54:46) δ = 1.23 (t, J = 6.9 Hz, 3H, a), 1.27 (t, J = 6.9 Hz, 3H, a), 1.32 (t, J = 7.2 Hz, 3H, b), 1.35 (t, J = 7.2 Hz, 3H, b), 1.68–2.06 (m, 1H, H-4, a/b), 2.06–2.30 (m, 1H, H-4, a/b), 2.30–3.00 (m, 5H, 2H-5, 1H-2 and 2H-7, a/b), 3.40–3.80 (m, 2H_{benzyl}, a/b), 3.80–4.25 (m, 6H, 1H-2, 4H CH_2OP and 1H-5', a/b), 4.50–4.66 (m, 1H, H-5', a/b), 5.08 (dd, J = 3.7, 8.7 Hz, 1 H-4', b), 5.28 (dd, J = 3.5, 8.7 Hz, 1H, H-4', a), 6.83–6.92 (m, 2H, b), 7.12–7.23 (m, 2H, a), 7.23–7.46 (m, 8H, a/b). ^{31}P NMR (CDCl_3 , 101.25 MHz) δ = 31.85 a/b not separable. Data for **7c**: ^1H NMR (CDCl_3 , 360 MHz) δ = 1.28 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.96–2.15 (m, 2H, H-4), 2.30–2.50 (m, 1H, H-5), 2.44 (s, 3H, Ts), 2.64 (dd, J_{AB} = 10.1 Hz, J_{PH} = 17.3 Hz, 1H, CH_2 -C-P), 2.76 (dd, J_{AB} = 10.1 Hz, J_{PH} = 8.3 Hz, 1H, CH_2 -C-P), 2.80–2.92 (m, 1H, H-5), 3.47 (dd, J_{AB} = 15.3 Hz, J_{PH} = 9.0 Hz, 1H, H-2), 3.58 (AB system, J_{AB} = 13.0 Hz, $\Delta\nu_{\text{AB}}$ = 29.9 Hz, 2H, PhCH_2N), 3.82 (AB system, J_{AB} = 15.3 Hz, $\Delta\nu_{\text{AB}}$ = 11.5 Hz, 1H, H-2), 4.00–4.20 (m, 4H, CH_2OP), 4.76 (AB system, J_{AB} = 16.6 Hz, $\Delta\nu_{\text{AB}}$ = 37.8 Hz, 2H, H_{benzyl}), 6.84–6.94 (m, 2H), 7.08–7.20 (m, 2H), 7.20–7.40 (m, 8H), 7.74 (d, J = 7.9 Hz, 2H). ^{13}C NMR (CDCl_3 , 90.56 Hz) δ = 16.4 (d, J_{PC} = 7.2 Hz, CH_3), 16.5 (d, J_{PC} = 5.8 Hz, CH_3), 21.5 (CH_3 , Ts), 29.4 (d, J_{PC} = 2.5 Hz, C-4), 45.6 (d, J_{PC} = 14.3 Hz, C-3), 49.95 (d, J_{PC} = 5.5 Hz, C-2), 51.6 (TsNCH₂ benzyl), 54.1 (d, J_{PC} = 3.8 Hz, C-5), 58.9 (CH_2 -NTs), 60.0 (NCH₂Ph), 62.1 (d, J_{PC} = 7.4 Hz, CH_2OP), 62.6 (d, J_{PC} = 7.2 Hz, CH_2OP), [18 arom C: 127.1 (CH), 127.3 (CH), 127.4 (2CH), 128.2 (2CH), 128.3 (2CH), 128.4 (2CH), 129.0 (2CH), 129.6 (2CH), 136.0 (Cq), 138.1 (Cq), 139.1 (Cq), 143.1 (Cq)]. ^{31}P NMR (CDCl_3 , 101.25 MHz) δ = 32.70.
- Data for **9c**: ^1H NMR (CDCl_3 , 250 MHz) δ = 1.27 (t, J = 7.0 Hz, 6H), 2.46 (s, 3H, CH_3 , Ts), 3.85–4.10 (m, 4H, CH_2OP), 4.24–4.35 (m, 2H, H-3), 4.32 (s, 2H, CH_2 benzyl), 5.45 (ddt, J_{PH} = 15.0 Hz, J = 13.2, 2.0 Hz, 1H, H-1), 6.33 (ddt, J_{PHtrans} = 51.7 Hz, J = 13.2, 6.0 Hz, 1H, H-2), 7.26–7.39 (m, 7H), 7.75 (d, J = 8.5 Hz, 2H). ^{13}C NMR (CDCl_3 , 62.9 Hz) δ = 16.3 (CH_3), 16.4 (CH_3), 21.6 (CH_3 , Ts), 47.8 (d, J_{PC} = 8.3 Hz, CH_2OP), 53.2 (CH_2 benzyl), 61.6 (d, J_{PC} = 5.5 Hz, C-3), 117.3 (d, J_{PC} = 182.1 Hz, C-1), [12 arom C: 127.4 (2CH), 127.8 (CH), 128.5 (2CH), 128.6 (2CH), 129.2 (CH), 136.0 (Cq), 136.1 (Cq), 143.6 (Cq)], 150.0 (d, J_{PC} = 2.8 Hz, C-2). ^{31}P NMR (CDCl_3 , 101.25 MHz) δ = 15.56.
- For a preparation of allylic phosphonates with a cross metathesis, see: He, A.; Yan, B.; Thanaravo, A.; Spilling, C. D.; Rath, N. P. *J. Org. Chem.* **2004**, 69, 8643–8651.
- Data for **12c**: ^1H NMR (CDCl_3 , 250 MHz) δ = 1.27 (t, J = 7.0 Hz, 6H), 2.43 (s, 3H, CH_3 , Ts), 3.80–3.88 (m, 2H, H-3), 3.88–4.05 (m, 4H, CH_2OP), 4.32 (s, 2H, CH_2 benzyl), 5.63 (dd, J_{PH} = 19.0 Hz, J_{trans} = 17.2 Hz, 1H, H-1), 6.39 (ddt, J_{PHcis} = 22.0 Hz, J_{trans} = 17.0 Hz, J = 5.2 Hz, 1H, H-2), 7.17–7.36 (m, 5H), 7.33 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H). ^{13}C NMR (CDCl_3 , 62.9 Hz) δ = 16.3 (CH_3), 16.4 (CH_3), 21.6 (CH_3 , Ts), 49.1 (CH_2OP), 49.5 (CH_2OP), 51.7 (CH_2 benzyl), 61.8 (d, J_{PC} = 5.5 Hz, C-3), 120.2 (d, J_{PC} = 187.2 Hz, C-1), [12 arom C: 127.2 (2CH), 128.1 (CH), 128.5 (2CH), 128.7 (2CH), 130.0 (2CH), 135.3 (Cq), 136.7 (Cq), 143.7 (Cq)], 146.1 (d, J_{PC} = 5.2 Hz, C-2). ^{31}P NMR (CDCl_3 , 101.25 MHz) δ = 16.52.
- Data for **13c**: ^1H NMR (CDCl_3 , 300 MHz) δ = 1.25 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 2.13 (dd, J = 9.3, J = 7.2 Hz, 1H, H-5), 2.36–2.65 (m, 3H, H-3, H-2 and H-4), 2.45 (s, 3H, Ts), 2.695 (dd, J = 9.3, 7.2 Hz, 1H, H-5), 2.80–2.94 (m, 1H, H-2), 3.37 (dd, J = 13.5, 3.0 Hz, 1H, CH_2 -NTs), 3.40–3.55 (m like AB system, 2H, Bn-N), 3.62 (dd, J = 13.5, 12.0 Hz, 1H, CH_2 -NTs), 3.93–4.08 (m, 4H, CH_2OP), 4.13 (d, J = 15.0 Hz, 1H, Bn-NTs), 4.32 (d, J = 15.0 Hz, 1H, Bn-NTs), 7.15–7.44 (m, 12H), 7.74 (d, J = 8.4 Hz, 2H). ^{13}C NMR (CDCl_3 , 90.56 Hz) δ = 16.4 (CH_3), 16.5 (CH_3), 21.5 (CH_3 , Ts), 36.9 (d, J_{PC} = 145.3 Hz, C-3), 38.3 (C-4), 50.5 (d, J_{PC} = 7.2 Hz, CH_2 -NTs), 53.9 (C-2), 54.0 (TsNCH₂Ph), 58.5 (d, J_{PC} = 5.6 Hz, C-5), 59.8 (NCH₂Ph), 61.5 (d, J_{PC} = 6.8 Hz, CH_2OP), 61.8 (d, J_{PC} = 6.7 Hz, CH_2OP), [18 arom C: 127.0 (CH), 127.4 (2CH), 127.8 (CH), 128.2 (2CH), 128.6 (4CH), 128.7 (2CH), 129.7 (2CH), 136.3 (Cq), 136.7 (Cq), 138.8 (Cq), 143.3 (Cq)]. ^{31}P

NMR (CDCl₃, 121.49 MHz) δ = 29.46. Data for **14c**: ¹H NMR (CDCl₃, 250 MHz) δ = 1.24 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.88 (dddd, ² J_{PH} = 16.5 Hz, J = 8.2, 8.2, 6.2 Hz, 1H, H-3) 2.17–2.66 (m, 4H, 2H-5, H-2 and H-4), 2.44 (s, 3H, Ts), 2.70–2.95 (m, 1H, H-2), 3.10 (dd, J = 4.8, 13.8 Hz, 1H, CH₂-NTs), 3.35 (dd, J = 10.2, 13.8 Hz, 1H, CH₂-NTs), 3.38–3.57 (m like AB system, 2H, Bn-N), 3.90–4.18 (m, 4H, CH₂OP), 4.16 (d, J = 15.2 Hz, 1H, Bn-NTs), 4.51 (d, J = 15.2 Hz, 1H, Bn-NTs), 7.20–7.50 (m, 12H), 7.74 (d, J = 8.2 Hz, 2H). ¹³C NMR (CDCl₃, 62.9 Hz) δ = 16.5 (CH₃), 16.6 (CH₃), 21.6 (CH₃, Ts), 38.1 (C-4), 38.2 (d, ¹ J_{PC} = 148.6 Hz, C-3), 52.8 (TsNCH₂), 53.0 (PhCH₂-NTs), 53.9 (C-2), 57.4 (d, ² J_{PC} = 5.9 Hz, C-5), 59.4 (NCH₂Ph), 61.8 (d, ² J_{PC} = 6.6 Hz, CH₂OP), 62.1 (d, ² J_{PC} = 6.6 Hz, CH₂OP), [18 arom C: 127.0 (CH), 127.4 (2CH), 127.8 (CH), 128.3 (2CH), 128.5 (2CH), 128.6 (4CH), 129.8 (2CH), 136.6 (2Cq), 138.8 (Cq), 143.4 (Cq)]. ³¹P NMR (CDCl₃, 101.25 MHz) δ = 30.94.

20. (a) Fadel, A.; Tesson, N. *Eur. J. Org. Chem.* **2000**, 2153–2159; (b) Fadel, A.; Tesson, N. *Tetrahedron: Asymmetry* **2000**, 11, 2023–2031.
21. Data for **15c**: ¹H NMR (CDCl₃, 360 MHz) δ = 1.26 (t, J = 7.0 Hz, 6H), 1.85–2.00 (m, 1H-4), 2.06–2.50 (m, 1H-4), 2.41 (s, 3H, Ts), 3.00–3.18 (m, 5H, 2H-5, 1H-2 and 2H, CH₂NTs), 3.82 (dd, J_{AB} = 14.4 Hz, ³ J_{PH} = 12.6 Hz, 1H, H-2), 4.00–4.15 (m, 4H, CH₂OP), 5.18 (br s, 2H, NH), 7.29 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H). ¹³C NMR (CDCl₃, 90.56 Hz) δ = 16.5 (d, ³ J_{PC} = 5.4 Hz, 2CH₃), 21.6 (CH₃, Ts), 31.6 (C-4), 45.5 (d, ¹ J_{PC} = 147.1 Hz, C-3), 46.7 (C-2), 46.9 (d, ³ J_{PC} = 6.9 Hz, C-5), 52.0 (CH₂NTs), 62.9 (d, ² J_{PC} = 7.2 Hz, 2CH₂OP), [6 arom C: 127.2 (2CH), 129.8 (2CH), 137.1 (Cq), 143.4 (Cq)]. ³¹P NMR (CDCl₃, 101.25 MHz) δ = 31.41.
22. For other possible deprotections of amine or hydrolysis of phosphonate function, see Refs. **11,20**.