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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.

1. Introduction

Vinylphosphonates have been known for several decades[1] 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 derivatives[5] 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]

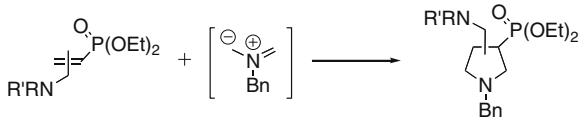
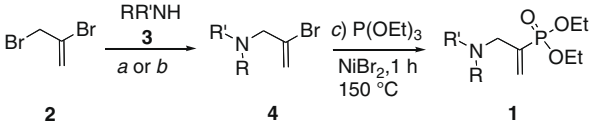


Figure 1. β- and γ-Aminopyrrolidinephosphonates.



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

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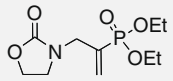
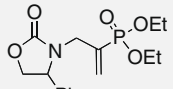
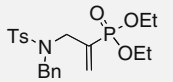
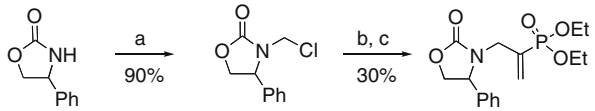
Table 1
Formation of vinylphosphonates **1a–c** produced via Scheme 1

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

[a] Reaction conditions: NaH, DMF, rt, 12 h.
[b] Cs_2CO_3, CH_3CN, reflux, 2 h.
[c] Solvent-free reaction of **4** with $P(OEt)_3$ 5 equiv, $NiBr_2$ 20 mol %, 150 °C, 1 h.



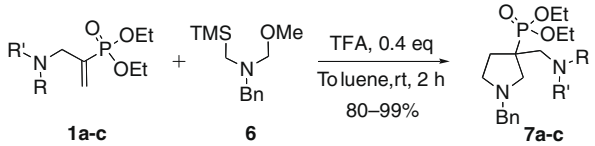
Scheme 2. Reagents and conditions: (a) $(CH_2O)_n$, TMSCl excess, reflux, 2 h; (b) NaH, $CH_2[P(O)(OEt)_2]_2$, THF, 0 °C; (c) NaH, $(CH_2O)_n$ 5 equiv, THF, rt.

It is noteworthy that the preparation of **1b** from oxazolidinone (±)-**3b** by chloromethylation [$(CH_2O)_n$/TMSCl] to afford oxazolidinone **5**, and subsequent alkylation [$CH_2(P(O)(OEt)_2)_2$] and vinylation [NaH/$(CH_2O)_n$][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]

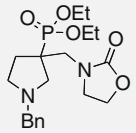
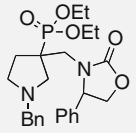
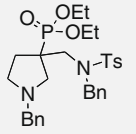
In order to expand the scope of our method, we decided to prepare the heterocyclic aminophosphonates via the cycloaddition of dipole derived from **6** with the *cis*- and *trans*-γ-aminophosphonates **9c** and **12c**, respectively. The preparation of *cis*-vinylphosphonate **9c** was achieved by alkylation of *N*-tosyl amine **6c** followed by phosphorylation to provide aminoalkynephosphonate **8c**. Subsequent Lindlar hydrogenation (5 wt % Pd on $CaCO_3$) 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 ($^3J_{PHtrans}$ = 51.7 Hz)

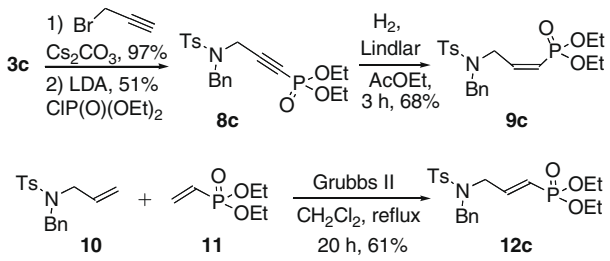


Scheme 3. β-Aminophosphonates by 1,3-dipolar cycloaddition.

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%.

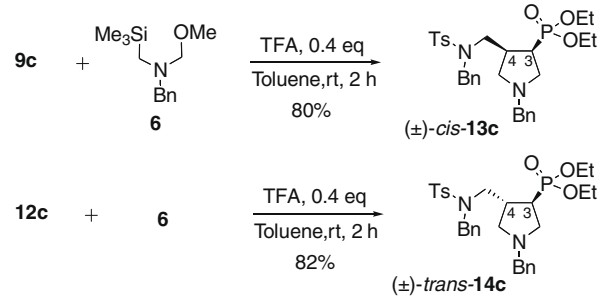


Scheme 4. Synthesis of γ-aminovinylphosphonates.

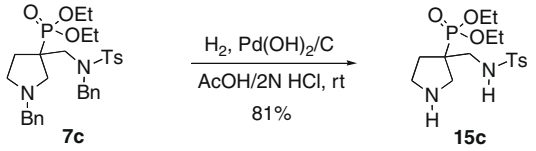
for **9c** and ($^3J_{PHcis}$ = 22.0 Hz) for **12c** are in agreement with the literature.[4c,d]

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 ^{13}C NMR spectra between P and CH_2–C-4. The observed values ($^3J_{PCcis}$ = 7.2 Hz) for **13c** and ($^3J_{PCtrans}$ = 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.

Acknowledgments

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14. *Data for* **1a**: ^{1}H 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, $^{2}J_{PHtrans}$ = 45.8 Hz, 1H, H-1), 6.13 (d, $^{2}J_{PHcis}$ = 22.0 Hz, 1H, H-1). ^{13}C NMR ($CDCl_3$, 90.56 Hz) δ = 16.2 (d, $^{3}J_{PC}$ = 6.2 Hz, CH_3), 16.4 (d, $^{3}J_{PC}$ = 6.1 Hz, CH_3), 44.3 (C-4′), 45.8 (d, $^{2}J_{PC}$ = 14.6 Hz, C-3), 61.8 (C-5′), 62.2 (d, $^{2}J_{PC}$ = 5.9 Hz, CH_2OP), 131.4 (d, $^{2}J_{PC}$ = 8.6 Hz, C-1), 134,5 (d, $^{1}J_{PC}$ = 177.1 Hz, C-2), 158.1 (C-2′). ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ = 16.44. *Data for* **1b**: ^{1}H 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, $^{3}J_{PHtrans}$ = 45.7 Hz, 1H, H-1), 6.17 (d, $^{3}J_{PHcis}$ = 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, $^{3}J_{PC}$ = 2.6 Hz, CH_3), 16.3 (d, $^{3}J_{PC}$ = 3.3 Hz, CH_3), 43.6 (d, $^{2}J_{PC}$ = 13.9 Hz, C-3), 59.0 (C-4′), 62.2 (d, $^{2}J_{PC}$ = 2.6 Hz, CH_2OP), 62.3 (d, $^{2}J_{PC}$ = 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, $^{2}J_{PC}$ = 7.9 Hz, C-1), 133.9 (d, $^{1}J_{PC}$ = 176.0 Hz, C-2), 157.8 (C-2′). ^{31}P NMR ($CDCl_3$, 145.78 MHz) δ = 16.52. *Data for* **1c**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 1.27 (t, J = 7.0 Hz, 6H), 2.47 (s, 3H), 3.88–4.10 (m, 6H, $2CH_2O$ and 2H-3), 4.39 (s, 2H, benzyl), 5.93 (d, $^{3}J_{PHtrans}$ = 46.8 Hz, 1H, H-1), 6.09 (d, $^{3}J_{PHcis}$ = 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, $^{2}J_{PC}$ = 19.9 Hz, C-3), 51.8 (CH_2 benzyl), 62.0 (d, $^{2}J_{PC}$ = 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, $^{2}J_{PC}$ = 7.1 Hz, C-1), 130.6 (d, $^{1}J_{PC}$ = 171.6 Hz, C-2). ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ = 17.00.
15. *Data for* **7a**: ^{1}H 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, $^{1}J_{PC}$ = 147.2 Hz, C-3), 46.5 (C-4′), 50.4 (C-2), 53.7 (d, $^{3}J_{PC}$ = 3.6 Hz, C-5), 58.6 (CH_2N), 59.6 (CH_2 benzyl), 61.9 (C-5′), 62.2 (d, $^{2}J_{PC}$ = 7.4 Hz, CH_2OP), 62.5 (d, $^{2}J_{PC}$ = 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**: ^{1}H 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**: ^{1}H 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, $^{3}J_{PH}$ = 17.3 Hz, 1H, CH_2–C–P), 2.76 (dd, J_{AB} = 10.1 Hz, $^{3}J_{PH}$ = 8.3 Hz, 1H, CH_2-C-P), 2.80–2.92 (m, 1H, H-5), 3.47 (dd, J_{AB} = 15.3 Hz, $^{3}J_{PH}$ = 9.0 Hz, 1H, H-2), 3.58 (AB system, J_{AB} = 13.0 Hz, $\Delta\nu_{AB}$ = 29.9 Hz, 2H, $PhCH_2N$), 3.82 (AB system, J_{AB} = 15.3 Hz, $\Delta\nu_{AB}$ = 11.5 Hz, 1H, H-2), 4.00–4.20 (m, 4H, CH_2OP), 4.76 (AB system, J_{AB} = 16.6 Hz, $\Delta\nu_{AB}$ = 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, $^{3}J_{PC}$ = 7.2 Hz, CH_3), 16.5 (d, $^{3}J_{PC}$ = 5.8 Hz, CH_3), 21.5 (CH_3, Ts), 29.4 (d, $^{2}J_{PC}$ = 2.5 Hz, C-4), 45.6 (d, $^{1}J_{PC}$ = 143.3 Hz, C-3), 49.95 (d, $^{2}J_{PC}$ = 5.5 Hz, C-2), 51.6 ($TsNCH_2$ benzyl), 54.1 (d, $^{3}J_{PC}$ = 3.8 Hz, C-5), 58.9 (CH_2-NTs), 60.0 (NCH_2Ph), 62.1 (d, $^{2}J_{PC}$ = 7.4 Hz, CH_2OP), 62.6 (d, $^{2}J_{PC}$ = 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.
16. *Data for* **9c**: ^{1}H 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, $^{2}J_{PH}$ = 15.0 Hz, J = 13.2, 2.0 Hz, 1H, H-1), 6.33 (ddt, $^{3}J_{PHtrans}$ = 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, $^{2}J_{PC}$ = 8.3 Hz, CH_2OP), 53.2 (CH_2 benzyl), 61.6 (d, $^{3}J_{PC}$ = 5.5 Hz, C-3), 117.3 (d, $^{1}J_{PC}$ = 182.1 Hz, C-1), [12 arom C: 127.4 (2CH), 127.8 (CH), 128.5 (2CH), 128.6 (2CH), 129.9 (2CH), 136.0 (Cq), 136.1 (Cq), 143.6 (Cq)], 150.0 (d, $^{2}J_{PC}$ = 2.8 Hz, C-2).^{31}P NMR ($CDCl_3$, 101.25 MHz) δ = 15.56.
17. 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.
18. *Data for* **12c**: ^{1}H 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, $^{2}J_{PH}$ = 19.0 Hz, J_{trans} = 17.2 Hz, 1H, H-1), 6.39 (ddt, $^{3}J_{PHcis}$ = 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, $^{3}J_{PC}$ = 5.5 Hz, C-3), 120.2 (d, $^{1}J_{PC}$ = 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, $^{2}J_{PC}$ = 5.2 Hz, C-2).^{31}P NMR ($CDCl_3$, 101.25 MHz) δ = 16.52.
19. *Data for* **13c**: ^{1}H 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, $^{1}J_{PC}$ = 145.3 Hz, C-3), 38.3 (C-4), 50.5 (d, $^{3}J_{PC}$ = 7.2 Hz, CH_2-NTs), 53.9 (C-2), 54.0 ($TsNCH_2Ph$), 58.5 (d, $^{3}J_{PC}$ = 5.6 Hz, C-5), 59.8 (NCH_2Ph), 61.5 (d, $^{2}J_{PC}$ = 6.8 Hz, CH_2OP), 61.8 (d, $^{2}J_{PC}$ = 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 ($CDCl_3$, 121.49 MHz) δ = 29.46. *Data for* **14c**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 1.24 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.88 (dddd, $^2J_{PH}$ = 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, CH_2-NTs), 3.35 (dd, J = 10.2, 13.8 Hz, 1H, CH_2-NTs), 3.38–3.57 (m like AB system, 2H, Bn-N), 3.90–4.18 (m, 4H, CH_2OP), 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). ^{13}C NMR ($CDCl_3$, 62.9 Hz) δ = 16.5 (CH_3), 16.6 (CH_3), 21.6 (CH_3, Ts), 38.1 (C-4), 38.2 (d, $^1J_{PC}$ = 148.6 Hz, C-3), 52.8 (TsNCH_2), 53.0 (PhCH_2-NTs), 53.9 (C-2), 57.4 (d, $^3J_{PC}$ = 5.9 Hz, C-5), 59.4 (NCH_2Ph), 61.8 (d, $^2J_{PC}$ = 6.6 Hz, CH_2OP), 62.1 (d, $^2J_{PC}$ = 6.6 Hz, CH_2OP), [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)]. ^{31}P NMR ($CDCl_3$, 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**: ^{1}H NMR ($CDCl_3$, 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, CH_2NTs), 3.82 (dd, J_{AB} = 14.4 Hz, $^3J_{PH}$ = 12.6 Hz, 1H, H-2), 4.00–4.15 (m, 4H, CH_2OP), 5.18 (br s, 2H, NH), 7.29 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 90.56 Hz) δ = 16.5 (d, $^3J_{PC}$ = 5.4 Hz, $2CH_3$), 21.6 (CH_3, Ts), 31.6 (C-4), 45.5 (d, $^1J_{PC}$ = 147.1 Hz, C-3), 46.7 (C-2), 46.9 (d, $^3J_{PC}$ = 6.9 Hz, C-5), 52.0 (CH_2NTs), 62.9 (d, $^2J_{PC}$ = 7.2 Hz, $2CH_2OP$), [6 arom C: 127.2 (2CH), 129.8 (2CH), 137.1 (Cq), 143.4 (Cq)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ = 31.41.
22. For other possible deprotections of amine or hydrolysis of phosphonate function, see Refs. 11,20.