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Diastereoselective synthesis of α,α′-disubstituted β-ketophosphonates derivatives as building blocks for automated syntheses

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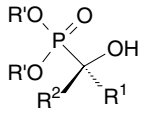
Abstract

A convenient and efficient synthesis of α,α′-disubstituted β-ketophosphonic derivatives in good to excellent *de*'s and yields has been achieved by α-acylation followed by diastereoselective α-alkylation of chiral 5-membered cyclic phosphonamidates.

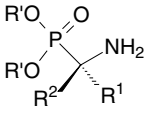
Keywords: Diastereoselection; Alkylation; 1,3,2-Oxazaphospholidine; β-Ketophosphonamidate

1. Introduction

The asymmetric synthesis of organophosphorus compounds is a relatively new field. The major factor stimulating the rapid development of the asymmetric synthesis of P-chiral organophosphorus compounds, during the past two decades, is their great practical value as ligands in catalysts for asymmetric organic synthesis. They are also important as biomolecules (enzyme inhibitors, antibiotics, antitumorals, herbicides and fungicides) and also in the study of the stereochemical course of reactions at stereogenic phosphorus [1]. Our goal was to find new methods for preparation of novel libraries of chiral difunctional compounds **1a** and **1b** in both enantiomeric forms as precursors for heterocyclic and peptidic syntheses. Compounds **1a** and **1b** have a quaternary chiral carbon center and two heteroatomic sites (either phosphoryl and hydroxyl groups or phosphoryl and amino groups) which can be used in further chemical manipulations.



1a



1b

From the retrosynthetic point of view, the target molecules (hydroxy **1a** and amino **1b**) can be obtained by anionotropic rearrangements (Baeyer–Villiger, Beckmann or Schmidt rearrangements) of the corresponding β-ketophosphonates **2**. Both rearrangements are stereospecific and are characterised.

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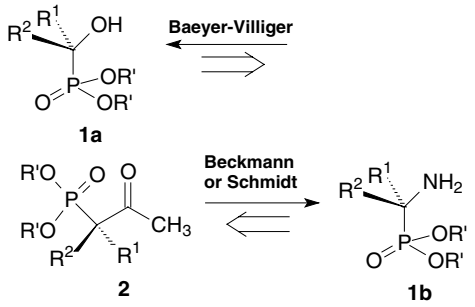


The α,α′-disubstituted β-ketophosphonates **2** can be obtained from the corresponding β-keto oxazaphospholidines **3**, which include the chiral framework necessary for induction of the chirality on the carbon α to phosphorus. Compound **3** can be prepared by diastereoselective C–C bond or C–fluoro bond formation with asymmetric induction (with asymmetric induction by chiral phosphorus atom) from α-monosubstituted precursors **4** (Scheme 1).

The synthesis of cyclic β-ketophosphonamidates **4** could be achieved by direct condensation of 2-*tert*-butylamino-1,2-diphenylethanol *unlike* **6** with various phosphonic dichlorides, followed by acylation of heterocycles **5** (Scheme 2).

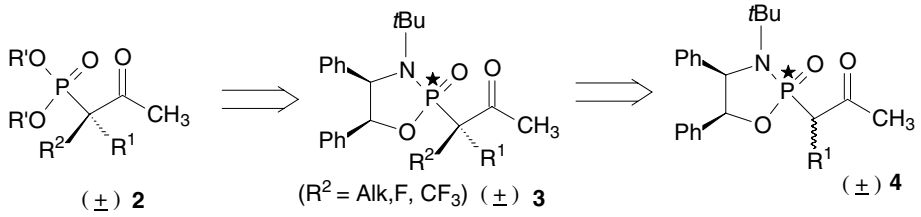
2. Results and discussion

2.1. Synthesis of 2-tert-butylamino-1,2-diphenyl-ethanol unlike 6

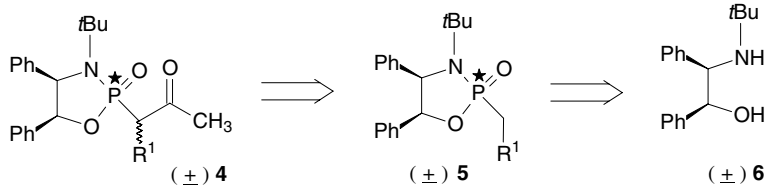
trans-Stilbene was epoxidised using dimethyldioxirane generated in situ in an oxone/$NaHCO_3$/acetone system [2]. Aminolysis with *tert*-butylamine in acetonitrile affords a racemic mixture of 2-*tert*-butylamino-1,2-diphenylethanol *unlike* **6** in 65% yield (Scheme 3).

2.2. Synthesis of phosphorus heterocycles 5

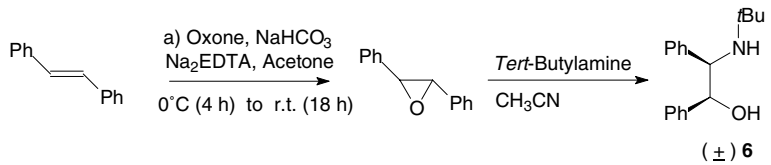
The cyclic phosphonamidates **5** are prepared, on a large scale, by combining the racemic 2-*tert*-butylamino-1,2-diphenylethanol *unlike* **6** with various phosphonic dichlorides. The diastereomeric phosphonamidates, **5** and **5′** (Table 1), were separated chromatographically and their structures were assigned using ^{31}P, ^{13}C and ^{1}H NMR spectroscopy. In case of compounds **5a** and **5′a** (R^1 = Me) as well as **5b** and **5′b** (R^1 = Ph) the X-ray crystallography confirmed the relative configuration of phosphorus atom of each diastereoisomer **5** and **5′** as the (RSRP/SRSP) and (RSSP/SRRP) diastereoisomers, respectively. However, the diastereomeric pairs can be more simply described as *cis* and *trans* isomers, respectively, referring to the relative



Scheme 1. Retrosynthesis of compounds **2**.

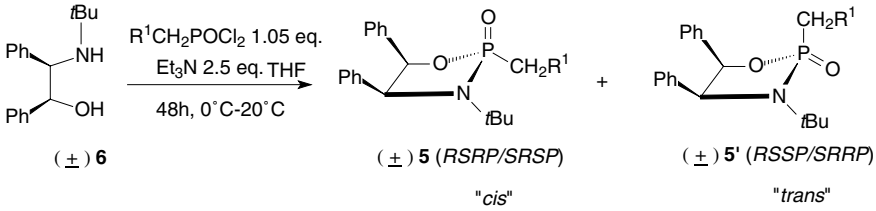


Scheme 2. Retrosynthesis of compounds **4**.



Scheme 3. Synthesis of 2-*tert*-butylamino-1,2-diphenyl-ethanol *unlike* **6**.

Table 1
Preparation of the phosphonamidates, **5** and **5′**

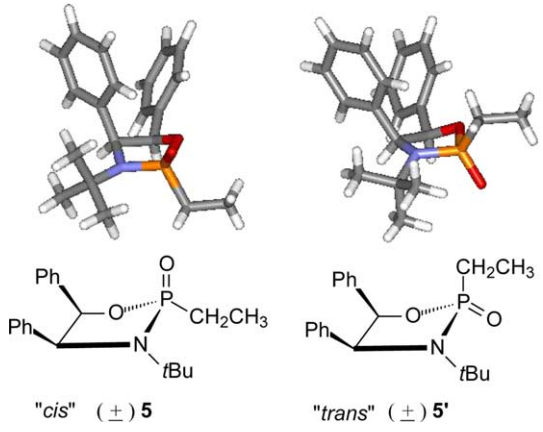


(±) **6** (±) **5** (*RSRP/SRSP*) "*cis*" (±) **5'** (*RSSP/SRRP*) "*trans*"

	R^1	**5/5′**	Yield (%)
a	Me	53/47[a]	96
b	Ph	57/43[a]	65
c	*i*Bu	54/46	88

[a] Structures **5** and **5′** determined by X-ray diffraction.

position of the two phenyl groups and of phosphoryl on the 5-membered ring.



2.3. Synthesis of the β-ketophosphonamidates *4*

The preparation of the β-ketophosphonamidates **4** involves acylation of the lithiated heterocycles *cis* **5**, using ethyl acetate at low temperature (Table 2).

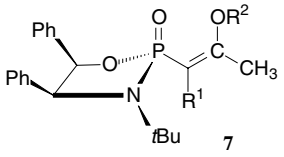
Acylation of the lithiated heterocycles *cis* **5**, and quenching the resulting carbanion with ethyl acetate affords the *cis*-β-ketophosphonamidates **4** with moderate yields (38–52% after purification) which was readily separated from the unreacted starting material by column chromatography [3]. The diastereoisomers **4***l* (major isomer) and **4***u* (minor isomer) were separated chromatographically, and their structures were assigned based on ^{31}P, ^{13}C and ^{1}H NMR spectroscopy. For compound **4***la* (R^1 = Me) the structure was confirmed by X-ray crystallography. The diastereoisomers **4***l***c** and **4***u***c** (R^1 = *i*Bu) were assigned by analogy using the spectrographic data. The acylation of the benzyl phosphonamidate (R^1 = Ph) led only to the enolic form of compound **4b**.

2.4. Alkylation of the cis-β-ketophosphonamidates *4*

The quaternary chiral carbon center is created by alkylation of potassium enolates of *cis*-β-ketophosphonamidates **4** (Scheme 4).

Denmark and Ambergey [5] have also demonstrated the importance of the conformation of such phosphorus heterocycles in controlling the diastereoselectivity of alkylation: The diastereoselectivity is higher in the *cis* series. Therefore, expecting a better diastereoselectivity, we investigated first the alkylation of the *cis* isomers of compounds **4**, using as a mixture of diastereoisomers **4***l* and **4***u*, since both will afford the same intermediate enolate (Table 3).

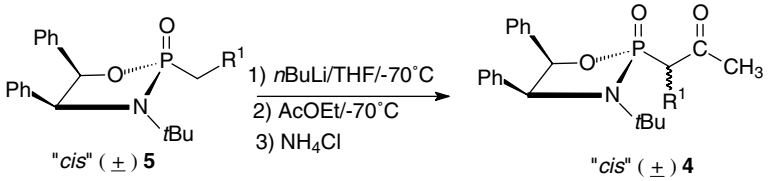
The *cis* compounds **3** were prepared in excellent yields (88–98%) (entries 1, 2, 5) and excellent diastereoselectivities for the new stereogenic center (entries 1, 2, 4, 5). Concerning entries 3 and 4, the yields decreased with the competitive formation of the O-alkylation products **7**. The structures of all compounds were assigned based on ^{31}P, ^{13}C, ^{1}H NMR spectroscopy.

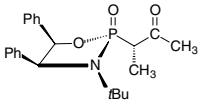
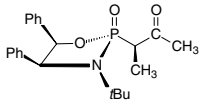
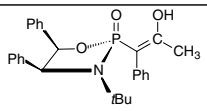
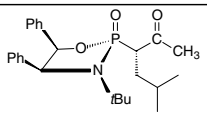
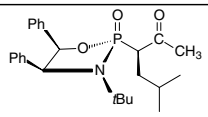


7

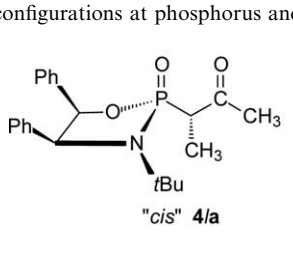
It must be pointed out that in the synthesis of a target compound **3**, with a precise chirality, the introduction order of the substituents is important: to obtain the best diastereoselectivity it is necessary to use a β-ketophosphonamidate **4**, as starting compound with the more

Table 2
Preparation of the *cis*-β-ketophosphonamidates **4** [3]



	R^1	Yield, %	*de*	Product **4** *l**	Product **4** *u**
a	Me	52	0		
b	Ph	38	-		
c	*i*Bu	50	88		

* *l* (*like*) and *u* (*unlike*) specify the relative configurations at phosphorus and α carbon atoms [4].



bulky group as R^1 substituent [entry 3: **3ac** *de* = 68% (R^1 = Me, R^2 = *i*Bu), entry 5: **3ca** *de* > 99% (R^1 = *i*Bu, R^2 = Me)].

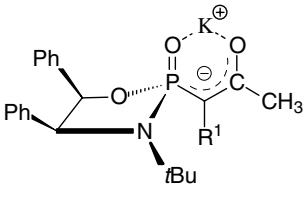
2.5. Preparation of fluorinated *cis*-β-ketophosphonamidates *3*

The fluorinated quaternary chiral center is created by reaction of potassium enolates of various *cis*-β-ketophosphonamidates **4** with Selectfluor and Umemoto reagent (Table 4).

For the fluoro and the tri-fluoromethyl derivatives, obtained, respectively, with Selectfluor (entries 6, 7) and Umemoto reagent (entry 8) the target compounds were easily separated by chromatography from the starting compounds.

For the fluoro compounds *de* are only 44% and 55% (entries 6, 7), but a simple chromatography allows to separate the two diastereoisomers.

The structures of all compounds were assigned by ^{31}P, ^{13}C, ^{1}H NMR (and ^{19}F NMR) spectroscopy and the correct configuration of compounds **3af** (R^1 = Me, R^2 = F) and **3fa** (R^1 = F, R^2 = Me) were determined by X-ray crystallography.



Scheme 4. Potassium enolate of the *cis*-β-ketophosphonamidates **4**.

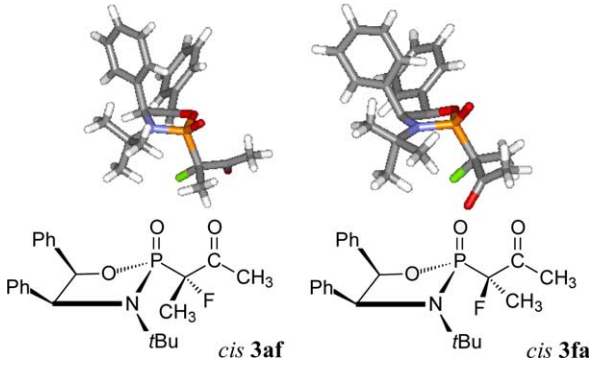
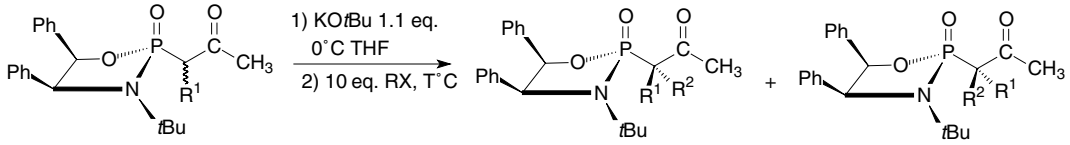


Table 3
Alkylation of the *cis*-β-ketophosphonamidates **4**



"*cis*" (±) **4**

"*cis*" (±) **3** (R^1,R^2) (major isomer)

"*cis*" (±) **3** (R^2,R^1) (minor isomer)

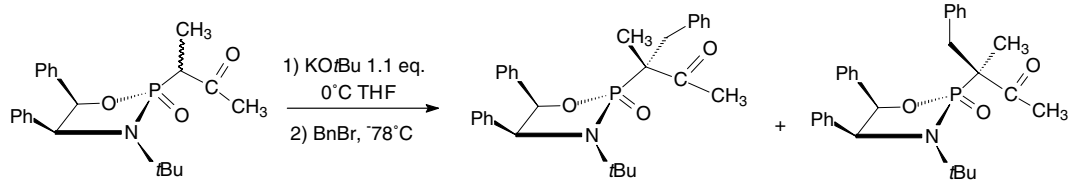
Entry		R^1		R^2	X	*T* (°C)	Yield (%)	*de*[a] (%)	Isolated compound
1	**a**	Me	**d**	Et	I	−30	90	87	**3ad**
2	**a**	Me	**e**	Bn	Br	−40	98	95	**3ae**
3	**a**	Me	**c**	*i*Bu	I	−40	60	68	**3ac** and **3ca**
4	**b**	Ph	**a**	Me	I	−50	80	>99	**3ba**
5	**c**	*i*Bu	**a**	Me	I	−50	88	>99	**3ca**

[a] Determined by ^{31}P NMR and or ^{1}H NMR.

Table 4
Preparation of fluorinated β-ketophosphonamidates **3**

Entry		R^1	No. eq. KO*t*Bu		R^2	No. eq. R^2X	*T* °C	Yield (%)	*de*[a] (%)	Isolated compound
6	**a**	Me	1.1	**f**	F (Selectfluor)	1.5	−70	91	55	**3af** and **3fa**[b]
7	**c**	*i*Bu	1.2	**f**	F (Selectfluor)	1.5	−70	63	44	**3cf** and **3fc**
8	**a**	Me	2	**g**	CF_3(Umemoto reagent) [6]	2	−70	38	94	**3ag**

[a] Determined by ^{19}F NMR.
[b] Structures **3af** (R^1 = Me and R^2 = F) and **3fa** (R^1 = F and R^2 = Me) determined by X-ray diffraction.



"*trans*" (±) **4'a**

"*trans*" (±) **3'ah**

"*trans*" (±) **3'ha**

Yield = 85%, *de* = 76

Scheme 5. Benzylation of the *trans* β-ketophosphonamidate **4**.

2.6. Comparison of the cis and trans series

To confirm that the diastereoselection is better in the *cis* series than in the *trans* series, the benzylation of the *trans* β-ketophosphonamidate **4′a** (R^1 = Me) was also performed (Scheme 5).

The yield was excellent (85%) but the diastereomeric excess 76% was less important than for the alkylation on the *cis*-β-ketophosphonamidate **4** (yield 98% and *de* 95%). This result can be explained by the steric crowding of the enolate faces less hindered in the transition state of the *trans* isomer in comparison with the *cis* isomer.

3. Conclusion

In summary, the alkylation or fluoration of β-ketophosphonamidates **4** proceeds with high selectivity and high yields, and provides access to pure diastereoisomers of α,α′-disubstituted β-ketophosphonamidates **3**. Further studies on the deprotection of α,α′-disubstituted β-ketophosphonamidates **3**, and on Baeyer–Villiger, Beckmann or Schmidt rearrangements of the corresponding α,α′-disubstituted β-ketophosphonates are currently in progress. Such reactions should lead to general and stereospecific syntheses of α,α-dialkylated α-hydroxy or α-aminophosphonates.

4. Experimental

4.1. General

^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra were recorded on a Bruker AC-200 spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million (ppm) and coupling constants in Hz downfield from internal tetramethylsilane. All solvents were distilled prior to use, and commercially available reagents used without further purification. All reactions were monitored by TLC (Merk, SIL G/UV_{254}); Merck silica gel (20–40 μm) was used for flash column chromatography and Merck silica gel (63–200 μm) for column chromatography. Melting points were determined using a Wild Leitz 350 and are given uncorrected. IR spectra were obtained with a Perkin–Elmer 377 spectrometer. Mass spectra were measured with a Jeol JMS DX-300 spectrometer. High resolution mass spectra were measured with a Jeol JMS SX-102 spectrometer.

4.2. Synthesis of (±)2-(tert-butylamino)-1,2-diphenylethanol unlike **6**

4.2.1. Synthesis of 2,3-diphenyloxirane

To a solution of *trans*-stilbene (32.22 g, 179 mmol) in (870 ml) CH_3CN and (456 ml) aqueous solution of EDTA (4×10^{-4} M), stirred at 0 °C, was added successively acetone (143 ml) then, every 15 min, by small scales, an homogenous mixture of Oxone® (269 g) and Na_2CO_3 (120 g) (time of addition: 1.30 h). After 6 h at 0 °C, the mixture was allowed to warm to room temperature during the night. The mixture was filtered, washed with 50 ml of CH_3CN. The filtrate was extracted by 800 ml of water. The water phase was extracted three times by 500 ml of ether. The organic phases were dried over $MgSO_4$ and evaporated under vacuum. The yellow viscous oil crystallised, washed with methanol, gave 25 g (98% yield) of yellow solid stored under nitrogen for the next synthetic step; m.p.: 68.1–69 °C (methanol), ^{1}H NMR $CDCl_3$: δ 7.38–7.42 (m, 10 H, CH_{ar}), 3.9 (s, 2 H, C*H*Ph), ^{13}C NMR $CDCl_3$: δ 137.12 (s, C_{ar}), 125.57 (s, C_{ar}H), 128.62 (s, C_{ar}H), 128.37 (s, C_{ar}H), 62.86 (s, *C*HPh), IR (CCl_4): ν 3065, 3031, 2980, 2924, 1499, 1455, 1029, yield: 98%.

4.2.2. Synthesis of (±)2-(tert-butylamino)-1,2-diphenylethanol unlike **6**

In a 250 ml batch were added (67.8 mmol, 13.3 g) of 2,3-diphenyloxirane, CH_3CN (50 ml), lithium perchlorate (14.4 g, 2 eq.) and *tert*-butyl amine (71.3 ml, 10 eq.). After 24 h at 80 °C, under agitation, the mixture was allowed to cool to room temperature. The reaction mixture evaporated under vacuum, gave a yellow oil. This oil was diluted with 100 ml of dichloromethane and 1 N aqueous HCl was added until pH 2. The organic phases were extracted two times with 50 ml of water. The water phase was extracted with ammonia. The water was then extracted with ethyl acetate. The organic phases dried over $MgSO_4$ and evaporated under vacuum gave 11.8 g of white solid, yield: 73%; m.p.: 56.7 °C (AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 270, ^{1}H NMR $CDCl_3$: δ 7.19–6.96 (m, 10 H, CH_{ar}), 4.68 (d, ^{3}J = 5.6, 1 H, HOC*H*Ph), 4.11 (d, ^{3}J = 5.6, 1 H, HNC*H*Ph), 1.00 (s, 9 H, *t*Bu), ^{13}C NMR $CDCl_3$: δ 142.39 (s, C_{ar}), 140.63 (s, C_{ar}H), 127.93–126.86 (10 C, C_{ar}H), 76.52 (s, *C* OH), 62.62 (s, *C*NH), 51.30 (s, $C(CH_3)_3$), 30.2 (s, CH_3), yield: 73%.

4.3. Synthesis of the 1,3,2-oxazaphospholidines **5**(cis) and **5′**(trans)

4.3.1. Synthesis of diethyl (3-methylbutyl)phosphonate [7]

Under N_2, are added (0.26 mol, 32 ml) *iso*-amylbromide and (0.275, 48 ml) triethyl phosphite. The mixture is stirred 40 h at 140 °C. The diethyl (3-methylbutyl)phosphonate is purified by distillation.

Boiling point: 100–110 °C (0.5 mmHg), IR (NaCl): ν 2990, 2910, 1270, 1040, ^{31}P NMR $CDCl_3$: δ 33.90 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 3.96 (qd, $^{3}J_{H-P}$ = 8.7, ^{3}J = 5.7, 4 H, CH_2, OCH_2CH$_3$), 1.5 (m, 5 H, PCH_2, PCH$_2$CH_2 and CH$_3$C*H*CH$_3$), 1.23 (t, ^{3}J = 5.7, 6 H, OCH$_2$CH_3), 0.80 (d, ^{3}J = 6.4, 6 H, CHCH_3), yield: 50%.

4.3.2. Synthesis of phosphonic dichlorides

4.3.2.1. General procedure [8]. In a 1 l one-necked pressure bottle equipped with a magnetic stirring bar were placed, under N_2, (0.12 mol, 26 g) of PCl_5, (65 mmol, 6.1 ml) of P(O)Cl_3 and (11.2 ml) of diethyl (3-methylbutyl)phosphonate. The pressure bottle was closed with a robber stopper and the mixture was heated in oil bath (110 °C) for 14 h. During this period the mixture rapidly became homogeneous. The mixture was allowed to cool to ambient temperature, transferred into a distillation flask and excess of P(O)Cl_3 was removed with a rotary evaporator at 35–40 °C for about 1 h. The crude product was purified by distillation under gradual heating.

4.3.2.2. (3-Methylbutyl)phosphonic dichloride. Boiling point: 88–95 °C (0.5 mmHg), ^{31}P NMR $CDCl_3$: δ 53.56 (s), ^{1}H NMR $CDCl_3$: δ 2.58 (m, 2 H, PCH_2), 1.71 [m, 3 H, $(CH_3)_2CHCH_2$ and $(CH_3)_2CHCH_2$], 0.90 [d, ^{3}J = 6.3, 6 H, CH_3], yield: 86%.

4.3.2.3. Benzylphosphonic dichloride. Boiling point: 108–115 °C (0.5 mmHg), ^{31}P NMR $CDCl_3$: δ 47.11 (s), ^{1}H NMR $CDCl_3$: δ 7.52–7.36 (M, 5 H, C_{ar}), 3.91 (d, $^{2}J_{H-P}$ = 18, 2 H, CH_2), yield: 100%.

4.3.3. General procedure for the synthesis of 1,3,2-oxazaphospholidines 2-oxides **5**(cis) and **5′**(trans)

In a 3-necked round flask (250 ml) equipped with a magnetic stirring bar were placed, under N_2, (5 g 18.6

ml) (±) 2-(*tert*-butylamino)-1,2-diphenylethanol *unlike* in (40 ml) THF and (5.45 ml, 39.06 mmol, 2.1 eq.) of triethylamine. The reaction mixture was allowed to cool to 0 °C. Then 1.05 eq. (19.53 mmol) of alkylphosphonic dichloride were added dropwise in (46 ml) of THF for 45 min. The mixture became rapidly heterogeneous and after stirring for 1 h at 0 °C, was allowed to return to ambient temperature for 48 h. The mixture was filtered and the precipitate was washed with 3×30 ml of THF. The organic phases dried over $MgSO_4$ and evaporated under vacuum gave orange oil. The crude product purified by flash chromatography on silica gel with CH_2Cl_2–EtOAc (100/0) as the starting eluent to CH_2Cl_2–EtOAc (60/40) gave the two diastereoisomers.

4.3.3.1. cis-3-tert-Butyl-2-ethyl-4,5-diphenyl-1,3,2-oxazaphospholidine 2-oxide (R^I = Me) ***5a***. Melting point: 167–168 °C (CH_2Cl_2/AcOEt), R_f: 0.48 (60/40 CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 344, HRMS FAB$^+$ (NBA) ($C_{20}H_{26}NO_2P$). Found: 344.1798. Calc.: 344.1779, IR (CH_2Cl_2): *v* 3050, 3010, 2980, 2920, 1650, 1453, 1266, 1213, 1069, 748, ^{31}P NMR (293 K) $CDCl_3$: δ 46.8 (s), ^{1}H NMR (293 K) $CDCl_3$: δ 8.06 (bs, 1 H, C*H*$_{ar}$), 7.26 (bs, 1 H, C*H*$_{ar}$), 7.06–6.94 (M, 6 H, C*H*$_{ar}$), 6.88 (bs, 1 H, C*H*$_{ar}$), 6.49 (bs, 1 H, C*H*$_{ar}$), 5.56 (d, ^3J = 5.9, 1 H, OC*H*Ph), 4.6 (dd, $^3J_{H-P}$ = 17.1, ^3J = 5.9, 1 H, NC*H*Ph), 2.32 (m, $^2J_{H-P}$ = 16.8, ^2J = 15.3, ^3J = 7.6, 1 H, C*H*$_2$CH$_3$), 2.07 (m, $^2J_{H-P}$ = 14.1, ^2J = 15.3, ^3J = 7.6, 1 H, C*H*$_2$CH$_3$), 1.34 (dt, $^3J_{H-P}$ = 19.7, ^3J = 7.6, 3 H, CH$_2$C*H*$_3$), 1.27 (s, 9 H, C*H*$_3$), ^{13}C NMR (293 K) $CDCl_3$: δ 138.9 (s, *C*$_{ar}$), 135.44 (d, $^3J_{C-P}$ = 8.18, *C*$_{ar}$), 128.37 (bs, *C*H$_{ar}$), 127.52–125.84 (*C*H$_{ar}$), 82.11 (s, O*C*HPh), 65.57 (d, $^2J_{C-P}$ = 8.2, N*C*HPh), 53.23 [d, $^2J_{C-P}$ = 5.6, *C*(CH$_3$)$_3$], 30.37 [d, $^3J_{C-P}$ = 2.6, C(*C*H$_3$)$_3$], 24.37 (d, $^1J_{C-P}$ = 124.3, *C*H$_2$CH$_3$), 8.14 (d, $^2J_{C-P}$ = 6.7, CH$_2$*C*H$_3$), yield: 62%.

4.3.3.2. trans-3-tert-Butyl-2-ethyl-4,5-diphenyl-1,3,2-oxazaphospholidine 2-oxide (R^I = Me) ***5′a***. Melting point: 154.9–155.6 °C (CH_2Cl_2/AcOEt), R_f: 0.3 (60/40 CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 344, HRMS FAB$^+$ (NBA) ($C_{20}H_{26}NO_2P$). Found: *m/z* $[M + H]^+$ 344.1773. Calc.: 344.1779, IR (CH_2Cl_2): *v* 3050, 3010, 2980, 2920, 1650, 1453, 1266, 1213, 1069, 748, ^{31}P NMR (293 K) $CDCl_3$: δ 49.7 (s), ^{1}H NMR (293 K) $CDCl_3$: δ 7.01–6.82 (M, 10H, C*H*$_{ar}$), 5.89 (d, ^3J = 6.3, 1 H, OC*H*Ph), 4.78 (dd, $^3J_{H-P}$ = 7.6, ^3J = 6.3, 1 H, NC*H*Ph), 2.34 (m, 2 H, C*H*$_2$CH$_3$), 1.45 (dt, $^3J_{H-P}$ = 20, ^3J = 7.6, 3 H, CH$_2$C*H*$_3$), 1.34 (s, 9 H, C*H*$_3$), ^{13}C NMR (293 K) $CDCl_3$: δ 139.6 (d, $^3J_{C-P}$ = 1.9, *C*$_{ar}$), 135.52 (d, $^3J_{C-P}$ = 11.2, *C*$_{ar}$), 127.70–126.46 (*C*$_{ar}$), 80.79 (s, O*C*HPh), 65.92 (d, $^2J_{C-P}$ = 5.5, N*C*HPh), 54.12 [d, $^2J_{C-P}$ = 3.3, *C*(CH$_3$)$_3$], 29.74 [d, $^3J_{C-P}$ = 2.9, C(*C*H$_3$)$_3$], 23.98 (d, $^1J_{C-P}$ = 130.6, *C*H$_2$CH$_3$), 8.19 (d, $^2J_{C-P}$ = 6.7, CH$_2$*C*H$_3$), yield: 26%.

4.3.3.3. cis-2-Benzyl-3-tert-butyl-4,5-diphenyl-1,3,2-oxazaphospholidine 2-oxide ***5b***. Melting point: 266.9–269.3 °C (CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 406, HRMS FAB$^+$ (NBA) ($C_{25}H_{29}NO_2P$). Found: *m/z* $[M + H]^+$ 406.1935. Calc.: 406.1936, IR ($CHCl_3$): *v* 3088, 3030, 2980, 2917, 1260, 1150, 1051, 754, ^{31}P NMR $CDCl_3$: δ 39.85 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 8.03 (bs, 1 H, C*H*$_{ar}$), 7.32–7.26 (M, 6 H, C*H*$_{ar}$), 7.06–6.77 (M, 7 H, C*H*$_{ar}$), 6.42 (bs, 1 H, C*H*$_{ar}$), 4.70 (d, ^3J = 5.9, 1 H, OC*H*Ph), 4.37 (dd, $^3J_{H-P}$ = 17.6, ^3J = 5.9, 1 H, NC*H*Ph), 3.63 (ABX system, δ_A = 3.74, δ_B = 3.57, $^2J_{P-H}$ = 21.9, $^2J_{P-H}$ = 17.1, ^2J = 15.4, 2 H, C*H*$_2$CH$_3$), 1.34 [s, 9 H, C(*C*H$_3$)$_3$], ^{13}C NMR $CDCl_3$: δ 138.56 (s, *C*$_{ar}$), 135.22 (d, $^3J_{C-P}$ = 8.2, *C*$_{ar}$), 133.01 (d, $^2J_{C-P}$ = 9.7, *C*$_{ar}$), 130.02–125.87 (*C*H$_{ar}$), 82.31 (s, O*C*HPh), 65.46 (d, $^2J_{C-P}$ = 8,2, N*C*HPh), 53.85 [d, $^2J_{C-P}$ = 5.6, *C*(CH$_3$)$_3$], 38.81 (d, $^1J_{C-P}$ = 119, *C*H$_2$Ph), 30.71 [d, $^3J_{C-P}$ = 2.6, C(*C*H$_3$)$_3$], yield: 47%.

4.3.3.4. trans-2-Benzyl-3-tert-butyl-4,5-diphenyl-1,3,2-oxazaphospholidine 2-oxide ***5′b***. Melting point: 130.8–131.9 °C (CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 406, HRMS FAB$^+$ (NBA) ($C_{25}H_{29}NO_2P$). Found: *m/z* $[M + H]^+$406.1951. Calc.: 406.1936, IR ($CHCl_3$): *v* 3088, 3030, 2980, 2917, 1260, 1150, 1051, 754, ^{31}P NMR $CDCl_3$: δ 42.93 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 7.53–7.36 (M, 5 H, C*H*$_{ar}$), 7.06–6.86 (M, 8 H, C*H*$_{ar}$), 6.50–6.47 (M, 2 H, C*H*$_{ar}$), 5.92 (d, ^3J = 6.6, 1 H, OC*H*Ph), 4.77 (t, ^3J = 6.6, 1 H, NC*H*Ph), 3.75 (ABX system, δ_A = 3.8, δ_B = 3.7, $^2J_{P-H}$ = 21.1, $^2J_{P-H}$ = 19.5, ^2J = 15.1, 2 H, C*H*$_2$Ph), 1.36 [s, 9 H, C(C*H*$_3$)$_3$], ^{13}C NMR $CDCl_3$: δ 139.33 (d, $^3J_{C-P}$ = 2.6, *C*$_{ar}$), 135.45 (d, $^3J_{C-P}$ = 11.5, *C*$_{ar}$), 130.37 (d, $^2J_{C-P}$ = 6.3, *C*$_{ar}$), 130.43–126.65 (*C*H$_{ar}$), 81.1 (s, O*C*HPh), 65.75 (d, $^2J_{C-P}$ = 5.2, N*C*HPh), 54.52 [d, $^2J_{C-P}$ = 3.3, *C*(CH$_3$)$_3$], 37.97 (d, $^1J_{C-P}$ = 124.6, *C*H$_2$Ph), 29.8 [d, $^3J_{C-P}$ = 3.3, C(*C*H$_3$)$_3$], yield: 18%.

4.3.3.5. cis-3-tert-Butyl-4,5-diphenyl-2-(3-methylbutyl)-1,3,2-oxazaphospholidine 2-oxide ***5c***. Melting point: 187.2–189 °C (CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 386, HRMS FAB$^+$ (NBA) ($C_{23}H_{33}NO_2P$). Found: *m/z* $[M + H]^+$ 386.2248. Calc.: 386.2249, IR ($CHCl_3$): *v* 3065, 3033, 2978, 2933, 1219, 1012, 754, ^{31}P NMR $CDCl_3$: δ 46.08 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 8.02 (bs, 1 H, C*H*$_{ar}$), 7.32–7.00 (M, 8 H, C*H*$_{ar}$), 6.45 (bs, 1 H, C*H*$_{ar}$), 5.55 (d, ^3J = 5.7, 1 H, OC*H*Ph), 4.59 (dd, $^3J_{H-P}$ = 17.1, ^3J = 5.7, 1 H, NC*H*Ph), 2.40–1.52 [M, 5 H, (CH$_3$)$_2$CHC*H*$_2$, (CH$_3$)$_2$C*H*CH$_2$ and C*H*$_2$P], 1.28 [s, 9 H, C(C*H*$_3$)$_3$], 0.94 [d, ^3J = 6.3, 6 H, (C*H*$_3$)$_2$CHCH$_2$], ^{13}C NMR $CDCl_3$: δ 138.92 (s, *C*$_{ar}$), 135.5 (d, $^3J_{C-P}$ = 8.2, *C*$_{ar}$), 128.67–125.91 (*C*H$_{ar}$), 82.04 (s, O*C*HPh), 65.68 (d, $^2J_{C-P}$ = 8.2, N*C*HPh), 53.34 [d, $^2J_{C-P}$ = 5.6, *C*(CH$_3$)$_3$], 32.59 (d, $^2J_{C-P}$ = 5.4, *C*H$_2$CH$_2$P), 30.47 [s, C(*C*H$_3$)$_3$], 29.46 (d, $^1J_{C-P}$ = 123, *C*H$_2$P), 28.98

[d, $^3J_{C-P}$ = 17.1, $(CH_3)_2CHCH_2$], 22.11 [s, $(CH_3)_2CHCH_2$], yield: 47%.

*4.3.3.6. trans-3-tert-Butyl-4,5-diphenyl-2-(3-methylbutyl)-1,3,2-oxazaphospholidine 2-oxide **5′c**.* Melting point: 130.4–131.5 °C (CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 386, HRMS FAB$^+$ (NBA) ($C_{23}H_{33}NO_2P$). Found: *m/z* $[M + H]^+$ 386.2260. Calc.: 386.2249, IR ($CHCl_3$): *v* 3065, 3033, 2978, 2933, 1219, 1012, 754, ^{31}P NMR $CDCl_3$: *δ* 49.08 (s, 1 P), ^{1}H NMR $CDCl_3$: *δ* 7.05–6081 (M, 10 H, C*H*$_{ar}$), 5.90 (d, ^3J = 6.3, 1 H, OC*H*Ph), 4.78 (dd, $^3J_{H-P}$ = 7.7, ^3J = 6.3, 1 H, NC*H*Ph), 2.35 (m, 2 H, C*H*$_2$P), 1.75 [M, 3 H, $(CH_3)_2CHCH_2$ and $(CH_3)_2CHCH_2$], 1.35 [s, 9 H, $C(CH_3)_3$], 0.99 [d, ^3J = 5.9, 6 H, $(CH_3)_2CHCH_2$], ^{13}C NMR $CDCl_3$: *δ* 139.62 (d, $^3J_{C-P}$ = 2.2, C_{ar}), 135.54 (d, $^3J_{C-P}$ = 11.2, C_{ar}), 127.71–126.45 (*C*H$_{ar}$), 80.86 (s, OCHPh), 65.84 (d, $^2J_{C-P}$ = 5.5, NCHPh), 54.15 [d, $^2J_{C-P}$ = 3.3, $C(CH_3)_3$], 32.59 (d, $^2J_{C-P}$ = 5.2, CH_2CH_2P), 29.79 [s, $C(CH_3)_3$], 28.87 (d, $^1J_{C-P}$ = 129, CH_2P), 28.89 [d, $^3J_{C-P}$ = 16.1 Hz, $(CH_3)_2CHCH_2$], 22.27 [s, $(CH_3)_2CHCH_2$], 21.94 [s, $(CH_3)_2CHCH_2$], yield: 41%.

4.4. Preparation of the β-ketophosphonamidates **4**

4.4.1. General procedure

In a 4-necked round flask (250 ml) equipped with a magnetic stirring bar were placed, under N_2, (4 g, 10 mmol) of the oxazaphospholidines, **5a** and **5b** in (50 ml) THF. The reaction mixture was allowed to cool to −78 °C before the drop wise addition of (7.25 ml, 1.1 eq.) *n*-BuLi (1.6 M). Then, after 30 min at −78 °C, the reaction mixture was dropwise transferred to a solution (10 ml, 10 eq.) of AcOEt in (50 ml) THF at −60 °C. The mixture was allowed to return to −40 °C for 30 min. Then the reaction mixture was allowed to return to ambient temperature for 15 h. The mixture was washed three times with 100 ml of ether. The organic phases dried over $MgSO_4$ and evaporated under vacuum gave a white solid. The solid, by flash chromatography on silica gel with CH_2Cl_2–EtOAc (100/0) as the starting eluent to CH_2Cl_2–EtOAc (60/40) gave the diastereoisomers.

*4.4.1.1. cis-3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)butan-2-one **4a**.* Melting point: 157.4–161.2 °C (hexane/AcOEt), R_f: 0.3 (60/40 hexane/AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 386, HRMS FAB$^+$ (NBA) ($C_{22}H_{29}NO_3P$). Found: *m/z* $[M + H]^+$ 386.1885. Calc.: 386.1885, IR ($CHCl_3$): *v* 3030, 3010, 2931, 2920, 1712, 1250, 1202, 1068, 765.

4la. ^{31}P NMR $CDCl_3$: *δ* 38.64 (s, 1 P), ^{1}H NMR $CDCl_3$: *δ* 7.98 (d L, ^3J = 7.7, 1 H, C*H*$_{ar}$), 7.26 (t L, ^3J = 7.4, 1 H, C*H*$_{ar}$), 7.06–6.89 (M, 7 H, C*H*$_{ar}$), 6.54 (d L, ^3J = 7.7, 1 H, C*H*$_{ar}$), 5.73 (d, ^3J = 6, 1 H, OC*H*Ph), 4.7 (dd, $^3J_{H-P}$ = 17.8, ^3J = 6, 1 H, NC*H*Ph), 3.71 [dq, $^2J_{H-P}$ = 20.3, ^3J = 7.2, 1 H, (O)CC*H*CH$_3$], 2.57 [s, 3 H, (O)CC*H*$_3$], 1.54 [dd, $^3J_{H-P}$ = 19.5, ^3J = 7.2, 3 H, (O)CCHC*H*$_3$], 1.33 [s, 9 H, C(C*H*$_3$)$_3$], ^{13}C NMR $CDCl_3$: *δ* 204.20 (d, $^2J_{C-P}$ = 4.1, *C*═O), 138.22 (d, $^2J_{C-P}$ = 0.7, C_{ar}), 135.06 (d, $^3J_{C-P}$ = 7.8, C_{ar}), 128.87–128.33 (bs, *C*H$_{ar}$), 127.61–125.92 (*C*H$_{ar}$), 83.82 (s, OCHPh), 65.78 (d, $^2J_{C-P}$ = 8.9, NCHPh), 54.19 [d, $^2J_{C-P}$ = 5.6, $C(CH_3)_3$], 52.39 [d, $^1J_{C-P}$ = 108.6, (O)CCHP], 31.11 [s, CHC(O)*C*H$_3$], 30.42 [d, $^3J_{C-P}$ = 2.4, C(*C*H$_3$)$_3$], 12.32 [d, $^2J_{C-P}$ = 4.84, C(O)CH*C*H$_3$].

4ub. ^{31}P NMR $CDCl_3$: *δ* 38.13 (s, 1 P), ^{1}H NMR $CDCl_3$: *δ* 7.98 (d L, ^3J = 7.7, 1 H, C*H*$_{ar}$), 7.26 (t L, ^3J = 7.4, 1 H, C*H*$_{ar}$), 7.06–6.89 (M, 7 H, C*H*$_{ar}$), 6.54 (d L, ^3J = 7.7, 1 H, C*H*$_{ar}$), 5.60 (d, ^3J = 6, 1 H, OC*H*Ph), 4.6 (dd, $^3J_{H-P}$ = 17, ^3J = 6, 1 H, NC*H*Ph), 3.7 [m, 1 H, (O)CC*H*CH$_3$], 2.37 [s, 3 H, (O)CC*H*$_3$], 1.56 [dd, $^3J_{H-P}$ = 18, ^3J = 7.2, 3 H, (O)CCHC*H*$_3$], 1.23 (s, 9 H, C(C*H*$_3$)$_3$), ^{13}C NMR $CDCl_3$: *δ* 206.06 (d, $^2J_{C-P}$ = 3.7, *C*═O), 138.42 (d, $^2J_{C-P}$ = 0.7, C_{ar}), 135.18 (d, $^3J_{C-P}$ = 8, C_{ar}), 128.87–128.33 (bs, *C*H$_{ar}$), 127.61–125.92 (*C*H$_{ar}$), 82.47 (s, OCHPh), 65.67 (d, $^2J_{C-P}$ = 8,9, NCHPh), 54.10 [d, $^2J_{C-P}$ = 5, $C(CH_3)_3$], 51.77 [d, $^1J_{C-P}$ = 111, (O)CCHP], 30.42 [d, $^3J_{C-P}$ = 2.4, C(*C*H$_3$)$_3$], 29.66 [s, CHC(O)*C*H$_3$], 13.46 (d, $^2J_{C-P}$ = 5.9, C(O)CH*C*H$_3$).

*4.4.1.2. (1Z)-1-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-1-phenylprop-1-en-2-ol **4b**.* Melting point: 117.8–118.5 °C (ether/pentane), MS FAB$^+$ (NBA) $[M + H]^+$: 448, HRMS FAB$^+$ (NBA) ($C_{27}H_{31}NO_3P$). Found: *m/z* $[M + H]^+$ 448.2052. Calc.: 448.2355, IR ($CHCl_3$): *v* 3510, 3080, 3010, 2960, 2930, 1613, 1230, 765, ^{31}P NMR $CDCl_3$: *δ* 39.06 (s, 1 P), ketone 2 diastereoisomers 33.54 et 33.47 (2s), ^{1}H NMR $CDCl_3$: *δ* 12.14 (s, 1 H, O*H*), 7.99 (bs, 1 H, C*H*$_{ar}$), 7.64–6.74 (M, 13 H, C*H*$_{ar}$), 6.37 (bs, 1 H, C*H*$_{ar}$), 4.62 (d, ^3J = 5,9, 1 H, OC*H*Ph), 4.31 (dd, $^3J_{H-P}$ = 17.8, ^3J = 6, 1 H, NC*H*Ph), 1.80 (s, 3 H, (HO)CC*H*$_3$), 1.29 [s, 9 H, C(C*H*$_3$)$_3$], ^{13}C NMR $CDCl_3$: *δ* 169.93 (d, $^2J_{C-P}$ = 5, (HO)*C*CH$_3$), 138.53 (s, C_{ar}), 135.33 (d, $^3J_{C-P}$ = 7.8, C_{ar}), 135.07 (d, $^3J_{C-P}$ = 26, C_{ar}), 128.92–125.9 (*C*H$_{ar}$), 99.45 (d, $^1J_{C-P}$ = 167, (O)C*C*HP), 83.15 (s, OCHPh), 64.94 (d, $^2J_{C-P}$ = 9.7, NCHPh), 54.34 [d, $^2J_{C-P}$ = 5.6, $C(CH_3)_3$], 30.15 [d, $^3J_{C-P}$ = 3, C(*C*H$_3$)$_3$], 20.03 (d, $^3J_{C-P}$ = 13.7, HOC(*C*H$_3$)).

*4.4.1.3. 3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-5-methylhexan-2-one **4lc**.* Melting point: 202.9–204.5 °C (hexane/AcOEt), MS FAB$^+$ (NBA) $[M + H]^+$: 428, HRMS FAB$^+$ (NBA) ($C_{27}H_{31}NO_3P$). Found: *m/z* $[M + H]^+$ 428.2351. Calc.: 428.2355, IR ($CHCl_3$): *v* 3060, 3010, 2940, 2920, 1720, 1238, ^{31}P NMR $CDCl_3$: *δ* 38.26 (s, 1 P), ^{1}H NMR $CDCl_3$: *δ* 7.98 (d L, ^3J = 7.9, 1 H, C*H*$_{ar}$), 7.26 (t L, ^3J = 7.6, 1 H, C*H*$_{ar}$), 7.06–6.96 (M, 6 H, C*H*$_{ar}$), 6.89 (t L, ^3J = 7.2, 1 H, C*H*$_{ar}$), 6.55 (d L, ^3J = 6.2, 1 H, C*H*$_{ar}$), 5.71 (d, ^3J = 6.1, 1 H, OC*H*Ph), 4.70 (dd, $^3J_{H-P}$ = 17.7, ^3J = 6.1, 1 H, NC*H*Ph), 3.73 [ddd, $^2J_{H-P}$ = 21.7,

$^3J = 2.2$, $^3J = 12$, 1 H, (O)CC*H*P], 2.54 [s, 3 H, (O)CCH_3], 2.32 (m, 1 H, CHCH_2CH), 1.60 (m, 2 H, CHCH_2CH and CH_3C*H*CH_3), 1,33 [s, 9 H, C(CH_3)$_3$], 0.97 (d, $^3J = 5$, 6 H, CH_3CHCH_3), ^{13}C NMR $CDCl_3$: δ 203.8 (d, $^2J_{C-P} = 4.8$, *C*=O), 138.29 (d, $^2J_{C-P} = 0.7$, C_{ar}), 135.1 (d, $^3J_{C-P} = 7.8$, C_{ar}), 128.9–128.28 (bs, *C*H$_{ar}$), 127.60–125.85 (*C*H$_{ar}$), 83.2 (s, O*C*HPh), 65.89 (d, $^2J_{C-P} = 8.9$, N*C*HPh), 56.85 (d, $^1J_{C-P} = 106.4$, *C*HP), 54.18 [d, $^2J_{C-P} = 5.4$, *C*(CH$_3$)$_3$], 35.91 (d, $^2J_{C-P} = 4.4$, *C*H$_2$CH(CH$_3$)$_2$), 31.84 [s, (O)*C*H$_3$], 30.48 [d, $^3J_{C-P} = 2.8$, C(*C*H$_3$)$_3$], 27.17 [d, $^3J_{C-P} = 16.1$, CH$_2$*C*H(CH$_3$)$_2$], 23.68 [s, CH$_2$CH(*C*H$_3$)$_2$], 21.32 [s, CH$_2$CH(*C*H$_3$)$_2$].

4.4.1.4. 3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-5-methylhexan-2-one ***4uc***. Melting point: 178–189 °C (hexane/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 428, IR ($CHCl_3$): *v* 3060, 3010, 2940, 2920, 1720, 1238, ^{31}P NMR $CDCl_3$: δ 36.90 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 7.96 (bs, 1 H, C*H*$_{ar}$), 7.26 (bs, 1 H, C*H*$_{ar}$), 7.07–6.91 (M, 7 H, C*H*$_{ar}$), 6.49 (bs, 1 H, C*H*$_{ar}$), 5.56 (d, $^3J = 6.1$, 1 H, OC*H*Ph), 4.58 (dd, $^3J_{H-P} = 18.2$, $^3J = 6$, 1 H, NC*H*Ph), 3.4 [ddd, $^2J_{H-P} = 20.6$, $^3J = 3.7$, $^3J = 11.2$, 1 H, (O)CC*H*P], 2.37 [s, 3 H, (O)CCH_3], 2.25 (m, 1 H, CHCH_2CH), 1.95 (m, 1 H, CHCH_2CH), 1.58 (m, 1 H, CH_3C*H*CH_3), 1.26 [s, 9 H, C(CH_3)$_3$], 0.96 [t, $^3J = 6.8$, 6 H, CH(CH_3)$_2$], ^{13}C NMR $CDCl_3$: δ 205.67 (d, $^2J_{C-P} = 4.3$, *C*=O), 138.46 (d, $^2J_{C-P} = 0.7$, C_{ar}), 135.14 (d, $^3J_{C-P} = 8.2$, C_{ar}), 128.78–128.36 (bs, *C*H$_{ar}$), 127.60–125.92 (*C*H$_{ar}$), 82.46 (s, O*C*HPh), 65.46 (d, $^2J_{C-P} = 9.1$, N*C*HPh), 56.64 (d, $^1J_{C-P} = 107.1$, *C*HP), 53.91 [d, $^2J_{C-P} = 5.4$, *C*(CH$_3$)$_3$], 37.56 [d, $^2J_{C-P} = 5$, *C*H$_2$CH(CH$_3$)$_2$], 30.50 [d, $^3J_{C-P} = 2.6$, C(*C*H$_3$)$_3$], 29.95 [s, (O)*C*H$_3$], 27.11 [d, $^3J_{C-P} = 14.1$, CH$_2$*C*H(CH$_3$)$_2$], 23.32 [s, CH$_2$CH(*C*H$_3$)$_2$], 21.19 [s, CH$_2$CH(*C*H$_3$)$_2$].

4.4.1.5. trans-3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)butan-2-one ***4′a***. Melting point: 148.7–150.7 °C, MS FAB$^+$ (NBA) [M + H]$^+$: 386, HRMS FAB$^+$ (NBA) ($C_{22}H_{29}NO_3P$). Found: *m*/*z* [M + H]$^+$ 385.1911. Calc.: 386.1885, IR ($CHCl_3$): *v* 3040, 3010, 2960, 2920, 1715, 1260, 1075, 760.

4′l a. ^{31}P NMR $CDCl_3$: δ 40.17 (s, 1 P), ^{1}H NMR (250 MHz) $CDCl_3$: δ 7.08–6.84 (M, 10 H, C*H*$_{ar}$), 5.94 (d, $^3J = 6.4$, 1 H, OC*H*Ph), 4.85 (dd, $^3J_{H-P} = 8.6$, $^3J = 6.4$, 1 H, NC*H*Ph), 3.65 (m, 1 H, C*H*CH$_3$), 2.42 [s, 3 H, C(O)CH$_3$], 1.73 (dd, $^3J_{H-P} = 19.5$, $^3J = 7.2$, 3 H, CHCH_3), 1.38 [s, 9 H, C(CH_3)$_3$], ^{13}C NMR $CDCl_3$: δ 204.64 (d, $^2J_{C-P} = 3$, *C*=O), 138.74 (s, C_{ar}), 135.08 (d, $^3J_{C-P} = 11.7$, C_{ar}), 128.08–1226.77 (*C*H$_{ar}$), 81.63 (s, O*C*HPh), 66.16 (d, $^2J_{C-P} = 6$, N*C*HPh), 54.75 (d, $^2J_{C-P} = 3.7$, *C*(CH$_3$)$_3$), 52.17 (d, $^1J_{C-P} = 113.5$, *C*HP), 29.96 [d, $^3J_{C-P} = 3.3$, C(*C*H$_3$)$_3$], 28.34 [s, (O)*C*H$_3$], 13.46 [d, $^2J_{C-P} = 5.6$, CH(*C*H$_3$)].

4′u b. ^{31}P NMR $CDCl_3$: δ 41,17 (s, 1 P), ^{1}H NMR (250 MHz) $CDCl_3$: δ 7.08–6.84 (M, 10 H, C*H*$_{ar}$), 5.92 (d, $^3J = 6.8$, 1 H, OC*H*Ph), 4.91 (dd, $^3J_{H-P} = 8.8$, $^3J = 6.8$, 1 H, NC*H*Ph), 3.65 (m, 1 H, C*H*CH$_3$), 2.51 [s, 3 H, C(O)CH$_3$], 1.72 (dd, $^3J_{H-P} = 19$, $^3J = 7.1$, 3 H, H$_{11}$), 1.37 [s, 9 H, C(CH_3)$_3$], ^{13}C NMR $CDCl_3$: δ 204.64 (d, $^2J_{C-P} = 3$, *C*=O), 138.76 (s, C_{ar}), 135.08 (d, $^3J_{C-P} = 11.7$, C_{ar}), 128.08–1226.77 (*C*H$_{ar}$), 81.26 (s, O*C*HPh), 65.84 (d, $^2J_{C-P} = 6.3$, N*C*HPh), 55.04 [d, $^2J_{C-P} = 3.3$, *C*(CH$_3$)$_3$], 52.58 [d, $^1J_{C-P} = 114.2$, *C*H(CH$_3$)], 29.62 [d, $^3J_{C-P} = 3.3$, CH(*C*H$_3$)], 28.9 [s, (O)*C*H$_3$], 13,68 [d, $^2J_{C-P} = 5.6$, CH(*C*H$_3$)].

4.5. Alkylation of the cis-β-ketophosphonamidates ***4****(l+u)*

4.5.1. General procedure

In a Schlenk (30 ml) equipped with a magnetic stirring bar were placed, under N_2, (0.5 mmol) of the *cis*-β-ketophosphonamidates **4** (l, u) in (6 ml) THF. The reaction mixture was allowed to cool to 0 °C before the addition of (62 mg, 0.55 mmol) *t*BuOK. Then, the reaction mixture was cooled to −60 °C for 5 min before the addition in 5 min of the alkylated agent (5 mmol). The mixture was maintained between −60 °C and −40 °C for 2 h. Then the reaction mixture was allowed to return to 20 °C and stirring for 15 h. The mixture was diluted with ether (20 ml), water (10 ml) and sodium thiosulfate 10% (20 ml). The water phase was extracted with 2×30 ml ether. The organic phases dried over $MgSO_4$ and evaporated under vacuum gave a solid. The solid, was purified by flash chromatography on silica gel with CH_2Cl_2–EtOAc (100/0) as the starting eluent to CH_2Cl_2–EtOAc (80/20).

4.5.1.1. cis-3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3-methylpentan-2-one ***3ad***. Melting point: 227.8–228.7 °C (CH_2Cl_2/AcOEt), R_f: 0.45 (90/10 CH_2Cl_2/AcOEt), MS FAB+ (NBA) [M + H]$^+$: 414, HRMS FAB$^+$ (NBA) ($C_{24}H_{33}NO_3P$). Found: *m*/*z* [M + H]$^+$ 414.2209. Calc.: 414.2198, IR ($CHCl_3$): *v* 3030, 3010, 2970, 2920, 1710, 1250, 1068, 760, ^{31}P NMR $CDCl_3$: δ 45.26 (s, 1 P) (other diastereoisomer 44.70), ^{1}H NMR $CDCl_3$: δ 8 (d L, $^3J = \text{up}3J = 7.7$, 1 H, C*H*$_{ar}$), 7.18 (t L, $^3J = 6.3$, 1 H, C*H*$_{ar}$), 7.03–6.96 (M, 6 H, C*H*$_{ar}$), 6.82 (t L, $^3J = 6.3$, 1 H, C*H*$_{ar}$), 6.45 (d L, $^3J = 7.7$, 1 H, C*H*$_{ar}$), 5.66 (d, $^3J = 5.6$, 1 H, OC*H*Ph), 4.66 (dd, $^3J_{H-P} = 17.5$, $^3J = 6.1$, 1 H, NC*H*Ph), 2.7 [m, 1 H, C*H*$_2$ (CH$_3$)], 2.55 [s, 3 H, C(O)CH_3], 2.15 [m, 1 H, C*H*$_2$(CH$_3$)], 1.50 [d, $^3J_{H-P} = 10.3$, 3 H, PC(*C*H$_3$)], 1.12 [s, 9 H, C(CH_3)$_3$], 0.82 [t, $^3J = 7.4$, 3 H, CH$_2$(CH_3)], ^{13}C NMR $CDCl_3$: δ 208.9 (d, $^2J_{C-P} = 3$, *C*=O), 138.74 (d, $^2J_{C-P} = 0.7$, C_{ar}), 135.34 (d, $^3J_{C-P} = 7.4$, C_{ar}), 128.83–125.87 (*C*H$_{ar}$), 83.02 (d, $^2J_{C-P} = 1.5$, O*C*HPh), 66.35 (d, $^2J_{C-P} = 8.2$, N*C*HPh), 60.14 (d, $^1J_{C-P} = 111$, P*C*CH$_3$), 53.7 [d, $^2J_{C-P} = 5.2$, *C*(CH$_3$)$_3$], 30.62 [d, $^3J_{C-P} = 2.6$, CH(*C*H$_3$)],

29.51 (d, $^2J_{C-P}$ = 6, $CH_2(CH_3)$), 28.24 [d, $^3J_{C-P}$ = 1.9, (O)CCH_3], 16.77 (d, $^2J_{C-P}$ = 1.1, PC(CH_3)), 9.02 (d, $^3J_{C-P}$ = 14.1, CH_2CH_3).

4.5.1.2. cis-3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3-phenylbutan-2-one ***3ae***. Melting point: 209–212 °C (CH_2Cl_2/AcOEt), R_f = 0.5 (95/10 CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 476, HRMS FAB$^+$ (NBA) ($C_{29}H_{34}NO_3P$). Found: *m/z* [M + H]$^+$ 476.2344. Calc.: 476.2355, IR ($CHCl_3$): *v* 3030, 3010, 2980, 2920, 1700, 1250, 1064, 760, ^{31}P NMR $CDCl_3$: δ 44.76 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 8.09 (d L, ^3J = 7.9, 1 H, CH_{ar}), 7.26–7.06 (M, 12 H, CH_{ar}), 6.85 (t L, ^3J = 6.5, 1 H, CH_{ar}), 6.50 (d L, ^3J = 7.5, 1 H, CH_{ar}), 5.69 (d, ^3J = 6, 1 H, OC*H*Ph), 4.70 (dd, $^3J_{H-P}$ = 17.3, ^3J = 6.1, 1 H, NC*H*Ph), 3.71 (AB system, δ_A = 4.0, δ_B = 3.4, $^3J_{P-HA}$ = 5.4, $^3J_{P-HB}$ = 10.7, ^2J = 14, 2 H, CH_2Ph), 2.62 [s, 3 H, C(O)CH_3], 1.47 [d, $^3J_{H-P}$ = 17.8, 3 H, PC(CH_3)], 1.23 [s, 9 H, C(CH_3)$_3$], ^{13}C NMR $CDCl_3$: δ 207.89 (d, $^2J_{C-P}$ = 1.1, *C*═O), 138.68 (d, $^2J_{C-P}$ = 0.7, C_{ar}), 136.28 (d, $^3J_{C-P}$ = 15.2, C_{ar}), 135.23 (d, $^3J_{C-P}$ = 7.8, C_{ar}), 130.2–125.9 (CH_{ar}), 82.75 (d, $^2J_{C-P}$ = 1.1, O*C*HPh), 66.54 (d, $^2J_{C-P}$ = 8.5, N*C*HPh), 60.56 (d, $^1J_{C-P}$ = 108, P*C*), 53.94 [d, $^2J_{C-P}$ = 5.2, *C*(CH$_3$)$_3$], 41.1 (d, $^2J_{C-P}$ = 3.7, *C*H$_2$Ph), 30.86 [d, $^3J_{C-P}$ = 2.6, C(*C*H$_3$)$_3$], 29.28 (d, $^3J_{C-P}$ = 6, (O)C*C*H$_3$), 18.6 [d, $^2J_{C-P}$ = 2.2, PC(*C*H$_3$)].

4.5.1.3. cis-3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3,5-dimethylhexan-2-one ***3ca***. Melting point: 234.6–235.4 °C (hexane/AcOEt), R_f: 0.15 (80/20 hexane/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 442, HRMS FAB$^+$ (NBA) ($C_{26}H_{37}NO_3P$). Found: *m/z* [M + H]$^+$ 442.2528. Calc.: 442.2511, IR ($CHCl_3$): *v* 3030,3010, 2970, 2920, 1710, 1240, ^{31}P NMR $CDCl_3$: δ 44.66 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 7.91 (d L, ^3J = 7.7, 1 H, CH_{ar}), 7.19 (t L, ^3J = 7.6, 1 H, CH_{ar}), 6.96–6.79 (M, 7 H, CH_{ar}), 6.5 (d L, ^3J = 7.7, 1 H, CH_{ar}), 5.62 (d, ^3J = 6, 1 H, OC*H*Ph), 4.63 (dd, $^3J_{H-P}$ = 16.7, ^3J = 6, 1 H, NC*H*Ph), 2.51 [s, 3 H, C(O)CH_3], 2.47 (m, 1 H, CH_2CH), 1.86 (m, 1 H, CH_2CH), 1.63 [d, $^3J_{H-P}$ = 18, 3 H, PC(CH_3)], 1.52 (m, 1 H, C*H* CH_2), 1.21 [s, 9 H, C(CH_3)$_3$], 0.95 [d, ^3J = 6.3, 3 H, CH(CH_3)$_2$], 0.88 [d, ^3J = 6.6, 3 H, CH(CH_3)$_2$], ^{13}C NMR $CDCl_3$: δ 207.46 (s, *C*═O), 138.67 (s, C_{ar}), 135.33 (d, $^3J_{C-P}$ = 8, C_{ar}), 128.97–125.67 (CH_{ar}), 82.09 (s, O*C*HPh), 65.87 (d, $^2J_{C-P}$ = 8.5, N*C*HPh), 59.14 (d, $^1J_{C-P}$ = 106, *C*P), 53.73 [d, $^2J_{C-P}$ = 5.2, *C*(CH$_3$)$_3$], 42.86 (d, $^2J_{C-P}$ = 3.5, *C*H$_2$CH), 30.95 [d, $^3J_{C-P}$ = 2.6, C(*C*H$_3$)$_3$], 28.11 [s, (O)C*C*H$_3$], 25.20 (d, $^3J_{C-P}$ = 14.1, CH$_2$*C*H), 25.06 [s, CH(*C*H$_3$)$_2$], 23,79 [s, CH(*C*H$_3$)$_2$], 19,74 (d, $^2J_{C-P}$ = 3, PC*C*H$_3$).

4.5.1.4. cis-3-tert-Butyl-4,5-diphenyl-2-[(1Z)-1-(1-methoxyethylidene)-3-methylbutyl]-1,3,2-oxazaphospholidine 2-oxide (O-alkylation product) ***7a***. R_f: 0.06 (80/20 hexane/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 442, ^{31}P NMR $CDCl_3$: δ 33,38 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 8 (bs, 1 H, CH_{ar}), 7.2 (bs, 1 H, CH_{ar}), 6.96–6.79 (M, 7 H, CH_{ar}), 6.5 (bs, 1 H, CH_{ar}), 6.02 (d, ^3J = 6,8, 1 H, OC*H*Ph), 4.70 (dd, $^3J_{H-P}$ = 16.9, ^3J = 6.5, 1 H, NC*H*Ph), 3.79 (s, 3 H, OCH_3), 2.55 (m, 1 H, CHCH_2), 2.06 (s, 3 H, OCCH_3), 2 (m, 2 H, CHH_2), 1.18 [s, 9 H, C(CH_3)$_3$], 1.02 [d, ^3J = 6.3, 3 H, CH(CH_3)$_2$], 0.90 [d, ^3J = 6.3, 3 H, CH(CH_3)$_2$], ^{13}C NMR $CDCl_3$: δ 162.36 (d, $^2J_{C-P}$ = 1.5, O*C*CH$_3$), 140.54 (s, C_{ar}), 136.93 (d, $^3J_{C-P}$ = 8.5, C_{ar}), 127.36–126.51 (CH_{ar}), 108.87 (d, $^1J_{C-P}$ = 106, *C* P), 82.23 (s, O*C*HPh), 65.80 (d, $^2J_{C-P}$ = 10.4, N*C*HPh), 54.98 (d, $^4J_{C-P}$ = 0.7, O*C*H$_3$), 53.39 [d, $^2J_{C-P}$ = 6.3, *C*(CH$_3$)$_3$], 39.39 (d, $^2J_{C-P}$ = 8.5, *C*H$_2$CH), 30.23 (d, $^3J_{C-P}$ = 3, C(*C*H$_3$)$_3$), 29.73 (s, *C*H(CH$_3$)$_2$],), 22.7 [s, CH(*C*H$_3$)$_2$], 22.15 [s, CH(*C*H$_3$)$_2$], 15.07 (d, $^3J_{C-P}$ = 11.7, [s, OC(*C*H$_3$)]).

4.5.1.5. cis-3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3,5-dimethylhexan-2-one ***3ac***. R_f: 0.147 (80/20 hexane/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 442, ^{31}P NMR $CDCl_3$: δ 45,53 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 8.08 (d L, ^3J = 7.9, 1 H, CH_{ar}), 7.24 (t L, ^3J = 7.4, 1 H, CH_{ar}), 7.04–6.79 (M, 7 H, CH_{ar}), 6.45 (d L, ^3J = 7.4, 1 H, CH_{ar}), 5.66 (d, ^3J = 6, 1 H, OC*H*Ph), 4.65 (dd, $^3J_{H-P}$ = 17.1, ^3J = 6, 1 H, NC*H*Ph), 2.62 [s, 3 H, C(O)CH_3], 2.51 (m, 2 H, CH_2CH), 2.1 (m, 1 H, C*H*CH$_2$), 1.55 [d, $^3J_{H-P}$ = 10, 3 H, PC(CH_3)], 1.14 [s, 9 H, C(CH_3)$_3$], 0.93 [d, ^3J = 6.5, 3 H, CH(CH_3)$_2$], 0.88 [d, ^3J = 6.8, 3 H, CH(CH_3)$_2$], ^{13}C NMR $CDCl_3$: δ 209.55 (d, $^2J_{C-P}$ = 2.2, *C*═O), 138.92 (s, C_{ar}), 135.44 (d, $^3J_{C-P}$ = 4, C_{ar}), 128.75–125.68 (CH_{ar}), 82.85 (s, O*C*HPh), 66.49 (d, $^2J_{C-P}$ = 8.2, N*C*HPh), 60.65 (d, $^1J_{C-P}$ = 107, *C*P), 53.74 [d, $^2J_{C-P}$ = 4.4, *C*(CH$_3$)$_3$], 43.98 (d, $^2J_{C-P}$ = 6, *C*H$_2$CH), 30.68 [d, $^3J_{C-P}$ = 2.6, C(*C*H$_3$)$_3$], 28.82 [s, (O)C*C*H$_3$], 25.85 (d, $^3J_{C-P}$ = 14.1, CH$_2$*C*H), 25 [s, CH(*C*H$_3$)$_2$], 23.96 [s, CH(*C*H$_3$)$_2$], 17.91 (d, $^2J_{C-P}$ = 2.2, PC*C*H$_3$).

4.5.1.6. cis-3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3-phenylbutan-2-one ***3ba***. Melting point 236.1–237.1 °C (hexane/AcOEt), R_f: 0.4 (90/10 CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 462, HRMS FAB$^+$ (NBA) ($C_{28}H_{33}NO_3P$). Found: *m/z* [M + H]$^+$ 462.2188. Calc.: 462.2198, IR ($CHCl_3$): *v* 3080, 3010, 2970, 2920, 1715, 1230, ^{31}P NMR $CDCl_3$: δ 41,90 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 7.98 (d L, ^3J = 7.4, 1 H, CH_{ar}), 7.74–6.73 (M, 13 H, CH_{ar}), 6.44 (d L, ^3J = 7.4, 1 H, CH_{ar}), 4.74 (d, ^3J = 6.1, 1 H, OC*H*Ph), 4.46 (dd, $^3J_{H-P}$ = 16.9, ^3J = 6.1, 1 H, OC*H*Ph), 2.50 [s, 3 H, C(O)CH_3], 2.18 (d, $^3J_{H-P}$ = 17, 3 H, PCCH_3), 1,.13 [s, 9 H, C(CH_3)$_3$], ^{13}C NMR $CDCl_3$: δ 204.86 (s, *C*═O), 138.73 (d, $^3J_{C-P}$ = 0.7, C_{ar}), 136.71 (d, $^3J_{C-P}$ = 4, C_{ar}), 135.4 (d, $^3J_{C-P}$ = 7.8, C_{ar}), 129.47–125.81 (CH_{ar}), 82.34 (s, O*C*HPh), 66.28 (d, $^2J_{C-P}$ = 8.5, N*C*HPh), 63.8 (d,

$^{1}J_{C-P}$ = 114, *C*P), 54.01 [d, $^{2}J_{C-P}$ = 5.2, *C*(CH_3)$_3$], 30.8 [d, $^{3}J_{C-P}$ = 2.6, C(*C*H_3)$_3$], 28 [s, (O)C*C*H_3], 20.95 (d, $^{2}J_{C-P}$ = 4.1, PC*C*H_3).

*4.5.1.7. cis-3-tert-Butyl-4,5-diphenyl-2-[(1Z)-2-methoxy-1-phenylprop-1-en-1-yl]-1,3,2-oxazaphospholidine 2-oxide (O-alkylation product) **7b**.* R_f: 0.1 (90/10 CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 442, ^{31}P NMR $CDCl_3$: δ 28.06 (s, 1 P), ^{1}H NMR $CDCl_3$: δ 8.3 (bs, 1 H, CH_{ar}), 7.3–6.84 (M, 13 H, CH_{ar}), 6.41 (bs, 1 H, CH_{ar}), 5.01 (d, ^{3}J = 6.1, 1 H, OC*H*Ph), 4.50 (dd, $^{3}J_{H-P}$ = 17.7, ^{3}J = 6.1, 1 H, NC*H*Ph), 3.88 (s, 3 H, OCH_3), 1.86 (s, 3 H, OCCH_3), 1.29 [s, 9 H, C(CH_3)$_3$], ^{13}C NMR $CDCl_3$: δ 165.12 (d, $^{2}J_{C-P}$ = 3, O*C*CH$_3$), 139.8 (s, C_{ar}), 137.86 (d, $^{2}J_{C-P}$ = 7, C_{ar}), 136.41 (d, $^{3}J_{C-P}$ = 8.1, C_{ar}), 131.76–126.19 (*C*H$_{ar}$), 111.91 (d, $^{1}J_{C-P}$ = 167.8, *C*P), 82.23 (d, $^{2}J_{C-P}$ = 1.1, O*C*HPh), 65.6 (d, $^{2}J_{C-P}$ = 10, N*C*HPh), 55.61 (d, $^{4}J_{C-P}$ = 1.1, OCH_3), 53.78 [d, $^{2}J_{C-P}$ = 6, *C*(CH_3)$_3$], 39.39 [d, $^{2}J_{C-P}$ = 8.5, C(*C*H_3)$_3$], 30.47 [d, $^{3}J_{C-P}$ = 3, C(*C*H_3)$_3$], 16.28 (d, $^{3}J_{C-P}$ = 11.2, OC*C*H_3).

*4.5.1.8. trans-3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3-phenylbutan-2-one **3′ah**.* Melting point: 187.8–189.8 °C (CH_2Cl_2/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 476, HRMS FAB$^+$ (NBA) ($C_{29}H_{35}NO_3P$). Found: *m*/*z* [M + H]$^+$ 476.2337. Calc.: 462.2355, ^{31}P NMR $CDCl_3$: δ 48.1 (s, 1 P), [other diastereoisomer: 48.4 (s, 1 P)], ^{1}H NMR $CDCl_3$: δ 7.26–6.93 (M, 15 H, CH_{ar}), 6 (d, ^{3}J = 7.1 H, OC*H*Ph), 5 (t, ^{3}J = 7, 1 H, NC*H*Ph), 3.69 (AB system, δ_A = 4.12, δ_B = 3.29, $^{3}J_{P-HA}$ = 4.4, $^{3}J_{P-HB}$ = 13, ^{2}J = 11.8, 2 H, CH_2Ph), 2.46 (s, 3 H, O=CCH_3), 1.66 (d, $^{3}J_{H-P}$ = 17.7, 3 H, PCCH_3), 1.42 [s, 9 H, C(CH_3)$_3$], ^{13}C NMR $CDCl_3$: δ 207.07 (s, *C*=O), 138.48 (d, $^{2}J_{C-P}$ = 2.8, C_{ar}), 136.66 (d, $^{3}J_{C-P}$ = 16, C_{ar}), 135.22 (d, $^{3}J_{C-P}$ = 11.3, C_{ar}), 130.6–126.84 (*C*H$_{ar}$), 81.18 (s, O*C*HPh), 66.01 (d, $^{2}J_{C-P}$ = 4.6, N*C*HPh), 58.15 (d, $^{1}J_{C-P}$ = 109.6, P*C*C=O), 55.5 [d, $^{2}J_{C-P}$ = 2.6, *C*(CH_3)$_3$], 40.1 (d, $^{2}J_{C-P}$ = 2.8, Ph*C*H$_2$), 30.12 [d, $^{3}J_{C-P}$ = 3.5, C(*C*H_3)$_3$], 29.58 (s, OC*C*H_3), 19,7 (d, $^{2}J_{C-P}$ = 3,9, PC*C*H_3).

4.6. Preparation of the fluorinated β-ketophosphonamidates **3**

4.6.1. General procedure

In a Schlenk (30 ml) equipped with a magnetic stirring bar were placed, under N_2, (0.5 mmol) of the *cis*-β-ketophosphonamidates **4** (l, u) in (6 ml) THF. The reaction mixture was allowed to cool to 0 °C before the addition of (62 mg, 0.55 mmol) *t*BuOK. Then, the reaction mixture was cooled to −60 °C for 5 min before the addition in 5 min of the fluoro or the tri-fluoromethyl derivatives (between 1.2 and 2 eq). The mixture was maintained between −70 °C for 2 h. Then the reaction mixture was allowed to return to 20 °C and stirring for 15 h. The mixture was diluted with ether (20 ml), water (30 ml). The water phase was extracted with 2 × 30 ml ether. The organic phases dried over $MgSO_4$ and evaporated under vacuum gave a solid. The solid, was purified by flash chromatography on silica gel with CH_2Cl_2–EtOAc (100/0) as the starting eluent to CH_2Cl_2–EtOAc (80/20). Mode opératoire générale.

*4.6.1.1. 3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3-fluorobutan-2-one **3af**.* Melting point: 211.5–212.8 °C (CH_2Cl_2/AcOEt), R_f: 0.4 (80/20 hexane/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 404, HRMS FAB$^+$ (NBA) ($C_{22}H_{28}FNO_3P$). Found: *m*/*z* [M + H]$^+$ 404.1768. Calc.: 404.1791, IR ($CHCl_3$): *v* 3030, 3010, 2970, 2920, 1725, 1260, 1102, 1066, 769, ^{31}P NMR $CDCl_3$: δ 32.45 (d, $^{2}J_{P-F}$ = 88.1, 1 P), ^{19}F NMR $CDCl_3$: δ −161.35 (d, $^{2}J_{F-P}$ = 88.1, 1 F), (dqd, $^{2}J_{F-P}$ = 88.1, $^{3}J_{F-H}$ = 23, $^{4}J_{F-H}$ = 2.5), ^{1}H NMR $CDCl_3$: δ 7.87 (d L, ^{3}J = 7.5, 1 H, CH_{ar}), 7.29–6.92 (M, 8 H, CH_{ar}), 6.43 (d L, ^{3}J = 7.4, 1 H, CH_{ar}), 5.79 (d, ^{3}J = 5.9, 1 H, OC*H*Ph), 4.69 (dd, $^{3}J_{H-P}$ = 15.6, ^{3}J = 5.9, 1 H, NC*H*Ph), 2.56 (d, $^{4}J_{H-F}$ = 2.5, 3 H, O=CCH_3), 1.98 (dd, $^{3}J_{H-P}$ = 14.4, $^{3}J_{H-F}$ = 23, 3 H, FCCH_3), 1.2 (s, 9 H, C(CH_3)$_3$), ^{13}C NMR $CDCl_3$: δ 203,3 (d, $^{2}J_{C-P}$ = 7.8, *C*=O), 138.3 (s, C_{ar}), 134.76 (d, $^{3}J_{C-P}$ = 8.5, C_{ar}), 128.03–125.87 (*C*H$_{ar}$), 100.66 (dd, $^{1}J_{C-F}$ = 200, $^{1}J_{C-P}$ = 135.8, F*C*), 82.71 (d, $^{2}J_{C-P}$ = 4, O*C*HPh), 66.05 (d, $^{2}J_{C-P}$ = 9, N*C*HPh), 54.22 [d, $^{2}J_{C-P}$ = 5.3, *C*(CH_3)$_3$], 30.45 [d, $^{3}J_{C-P}$ = 1.3, C(*C*H_3)$_3$], 26.85 (s, OC*C*H_3), 22.09 (d, $^{2}J_{C-P}$ = 23, FC*C*H_3).

*4.6.1.2. 3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3-fluorobutan-2-one **3fa**.* Melting point: 213.6–214.4 °C (CH_2Cl_2/AcOEt), R_f: 0.3 (80/20 hexane/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 404, HRMS FAB$^+$ (NBA) ($C_{22}H_{28}FNO_3P$). Found: *m*/*z* [M + H]$^+$ 404.1768. Calc.: 404.1791, IR ($CHCl_3$): *v* 3030, 3010, 2970, 2920, 1725, 1260, 1102, 1066, 769, ^{31}P NMR $CDCl_3$: δ 32.14 (d, $^{2}J_{P-F}$ = 89, 1 P), ^{19}F NMR $CDCl_3$: δ −158.91 (d, $^{2}J_{F-P}$ = 89, 1 F), (dqd, $^{2}J_{F-P}$ = 89, $^{3}J_{F-H}$ = 22.5, $^{4}J_{F-H}$ = 3.5), ^{1}H NMR $CDCl_3$: δ 7.8 (d L, ^{3}J = 7.4, 1 H, CH_{ar}), 7.29-6.83 (M, 8 H, CH_{ar}), 6.45 (d L, ^{3}J = 7.4, 1 H, CH_{ar}), 5.82 (d, ^{3}J = 5.9, 1 H, OC*H*Ph), 4.64 (dd, $^{3}J_{H-P}$ = 15.8, ^{3}J = 5.9, 1 H, NC*H*Ph), 2.56 (d, $^{4}J_{H-F}$ = 3.5, 3 H, O=CCH_3), 1.97 (dd, $^{3}J_{H-P}$ = 15.1, $^{3}J_{H-F}$ = 22.5, 3 H, FCCH_3), 1.26 (s, 9 H, C(CH_3)$_3$), ^{13}C NMR $CDCl_3$: δ 203.57 (d, $^{2}J_{C-P}$ = 4.4, *C*=O), 138.16 (s, C_{ar}), 134.7 (d, $^{3}J_{C-P}$ = 8.9, C_{ar}), 128.21–125.84 (*C*H$_{ar}$), 100.23 (dd, $^{1}J_{C-F}$ = 201, $^{1}J_{C-P}$ = 137.3, F*C*), 81.88 (d, O*C*HPh), 65.52 (d, $^{2}J_{C-P}$ = 9.3, N*C*HPh), 54.05 [d, $^{2}J_{C-P}$ = 5.2, *C*(CH_3)$_3$], 30.68 (d, C(*C*H_3)$_3$), 26.91 (s, OC*C*H_3), 21.72 (d, $^{2}J_{C-P}$ = 22.3, FC*C*H_3).

*4.6.1.3. 3-(3-tert-butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3-fluoro-5-methylhexan-2-one **3fc**.* Melting point: 201.5–204.3 °C (hexane/AcOEt), R_f: 0.1 (80/20 hexane/AcOEt), MS FAB$^+$ (NBA) [M + H]$^+$: 446, HRMS

FAB^+ (NBA) ($C_{25}H_{34}FNO_3P$). Found: *m/z* $[M + H]^+$ 446.2245. Calc.: 446.2260, ^{31}P NMR $CDCl_3$: δ 32.08 (d, $^2J_{P-F} = 91$, 1 P), NMR ^{19}F NMR $CDCl_3$: δ −169.61 (d, $^2J_{F-P} = 91$, 1 F), (ddd, $^2J_{F-P} = 91$, $^3J_{F-H} = 7$, $^3J_{F-H} = 44$), ^1H NMR $CDCl_3$: δ 7.84 (d L, $^3J = 7.5$, 1 H, CH_{ar}), 7.25–6.85 (M, 8 H, CH_{ar}), 6.44 (d L, $^3J = 7.5$, 1 H, CH_{ar}), 5.77 (d, $^3J = 6$, 1 H, OC*H*Ph), 4.69 (dd, $^3J_{H-P} = 15.6$, $^3J = 6$, 1 H, NC*H*Ph), 2.6 (m, 1 H, CHCH_2), 2.55 (d, $^4J_{H-F} = 2.2$, 3 H, O=CCH_3), 2.3 (m, 1 H, CHCH_2), 1.83 (m, 1 H, C*H*CH$_2$), 1.19 [s, 9 H, C(CH_3)$_3$], 1 (d, $^3J = 7$, 3 H, CH_3CHCH_3), 0.94 (d, $^3J = 7$, 3 H, CH_3CHCH_3), ^{13}C NMR $CDCl_3$: δ 203.64 (d, $^2J_{C-P} = 4.3$, *C*=O), 138.48 (s, C_{ar}), 134.9 (d, $^3J_{C-P} = 8.9$, C_{ar}), 128.2–125.83 (*C*H$_{ar}$), 104.62 (dd, $^1J_{C-F} = 203.6$, $^1J_{C-P} = 132.6$, *C*F), 82.5 (d, $^2J_{C-P} = 4$, OC*H*Ph), 65.93 (d, $^2J_{C-P} = 9.1$, NC*H*Ph), 54.2 [d, $^2J_{C-P} = 5$, *C*(CH$_3$)$_3$], 42.68 (d, $^2J_{C-P} = 19.5$, CH*C*H$_2$), 30.46 [s, C(*C*H$_3$)$_3$], 27.96 (s, *C*H$_3$CH*C*H$_3$), 25.45 (d, $^3J_{C-P} = 9$, CH$_3$*C*HCH$_3$), 24.32 (s, *C*H$_3$CH*C*H$_3$), 23 (d, $^3J_{C-P} = 3.5$, OC*C*H$_3$).

4.6.1.4. 3-(3-tert-butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-3-fluoro-5-methylhexan-2-one ***3cf***. Melting point: 205.2–206 °C (hexane/AcOEt), R_f: 0.11 (80/20 hexane/AcOEt), MS FAB^+ (NBA) $[M + H]^+$: 446, HRMS FAB^+ (NBA) ($C_{25}H_{34}FNO_3P$). Found: *m/z* $[M + H]^+$ 446.2245. Calc.: 446.2260, ^{31}P NMR $CDCl_3$: δ 31.84 (d, $^2J_{P-F} = 92$, 1 P), ^{19}F NMR $CDCl_3$: δ −167.1 (d, $^2J_{F-P} = 92$, 1 F), (ddd, $^2J_{F-P} = 92$, $^3J_{F-H} = 10$, $^3J_{F-H} = 40$), ^1H NMR $CDCl_3$: δ 7.84 (d L, $^3J = 7.5$, 1 H, CH_{ar}), 7.25–6.85 (M, 8 H, CH_{ar}), 6.44 (d L, $^3J = 7.5$, 1 H, CH_{ar}), 5.75 (d, $^3J = 5.7$, 1 H, OC*H*Ph), 4.69 (dd, $^3J_{H-P} = 15.6$, $^3J = 5.7$, 1 H, NC*H*Ph), 2.41 (m, 1 H, CHCH_2), 2.3 (d, $^4J_{H-F} = 2.9$, 3 H, O=CCH_3), 2.3 (m, 1 H, CHCH_2), 1.83 (m, 1 H, C*H*CH$_2$), 1.28 [s, 9 H, C(CH_3)$_3$], 1.03 (d, $^3J = 6.8$, 3 H, CH_3CHCH_3), 0.98 (d, $^3J = 6.8$, 3 H, CH_3CHCH_3), ^{13}C NMR $CDCl_3$: δ 203.21 (d, $^2J_{C-P} = 4.5$, *C*=O), 138.27 (s, C_{ar}), 134.73 (d, $^3J_{C-P} = 8.9$, C_{ar}), 128.2–125.83 (*C*H$_{ar}$), 104.23 (dd, $^1J_{C-F} = 205$, $^1J_{C-P} = 132.5$, *C*F), 81.83 (s, OC*H*Ph), 65.46 (d, $^2J_{C-P} = 9.3$, NC*H*Ph), 54.12 [d, $^2J_{C-P} = 5$, *C*(CH$_3$)$_3$], 42.68 (d, $^2J_{C-P} = 19.5$, CH*C*H$_2$), 30.79 [s, C(*C*H$_3$)$_3$], 26.98 (s, *C*H$_3$CH*C*H$_3$), 25.25 (d, $^3J_{C-P} = 11.5$, CH$_3$*C*HCH$_3$), 24.12 (s, *C*H$_3$CH*C*H$_3$), 23.3 (d, $^3J_{C-P} = 3,5$, OC*C*H$_3$).

4.6.1.5. 3-(3-tert-Butyl-4,5-diphenyl-2-oxo-1,3,2-oxazaphosphorinan-2-yl)-4,4,4-trifluoro-3-methylbutan-2-one ***3ag***. Melting point: 209.7–211.4 °C (CH_2Cl_2), R_f: 0,28 (100% CH_2Cl_2), MS FAB^+ (NBA) $[M + H]^+$: 454, HRMS FAB^+ (NBA) ($C_{23}H_{28}F_3NO_3P$). Found: *m/z* $[M + H]^+$ 454.1778. Calc.: 454.1759, IR ($CHCl_3$): *v* 3050, 3010, 2970, 2920, 1720, 1220, 1170, 1060, 765, ^{31}P NMR $CDCl_3$: δ 31.39 (q, $^3J_{P-F} = 7$, 1 P), ^{19}F NMR $CDCl_3$: δ −62.94 (d, $^3J_{F-P} = 7$, 3 F), ^1H NMR $CDCl_3$: δ 7.84 (d L, $^3J = 7.9$, 1 H, CH_{ar}), 7.2 (t L, $^3J = 6$, 1 H, CH_{ar}), 7.03–6.88 (M, 7 H, CH_{ar}), 6.57 (d L, $^3J = 7.7$, 1 H, CH_{ar}), 5.8 (d, $^3J = 5.9$, 1 H, OC*H*Ph), 4.71 (dd, $^3J_{H-P} = 17.3$, $^3J = 5.9$, 1 H, NC*H*Ph), 2.67 (s, 3 H, OCCH_3), 1.78 (d, $^3J_{H-P} = 17$, 3 H, PCCH_3), 1.16 [s, 9 H, C(CH_3)$_3$], ^{13}C NMR $CDCl_3$: δ 199.3 (s, *C*=O), 137.87 (s, C_{ar}), 134.59 (d, $^3J_{C-P} = 8.7$, C_{ar}), 128.76–125.61 (*C*H$_{ar}$), 127 (qd, $^1J_{C-F} = 283$, $^2J_{C-P} = 2.6$, *C*F$_3$), 82.1 (s, OC*H*Ph), 66 (d, $^2J_{C-P} = 9.8$, NC*H*Ph), 64.61 (dq, $^1J_{C-P} = 107$, $^2J_{C-F} = 24$, *C*CF$_3$), 54.57 [d, $^2J_{C-P} = 4.8$, *C*(CH$_3$)$_3$], 30.49 [d, $^3J_{C-P} = 2.6$, C(*C*H$_3$)$_3$], 29.02 (s, OC*C*H$_3$), 16.61 (t, $^2J_{C-P} = 2.8$, *C*H$_3$CHCF$_3$).

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