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# Diastereoselective Michael addition of 2*H*-2-oxo-1,4,2-oxaza phosphinanes to olefins

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ABSTRACT

Diastereoselective Michael additions of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes to olefins were described. Phosphinopeptide compounds were obtained in very good yield (up to 90%) and diasteromeric excesses ranging from 26 to 78%.



## 1. Introduction

As a part of our search for new biologically active compounds in the field of human health or plant protection, we are interested in introducing P–C-heteroatom framework into heterocyclic structures. According to literature, there are still a few general methods for the formation or modification of phosphorus heterocycles.[1a] On the other hand, aminophosphinic acids and their derivatives play an important role as metal-complexing agents and have a range of diagnostic and therapeutic applications (Fig. 1).[1b]

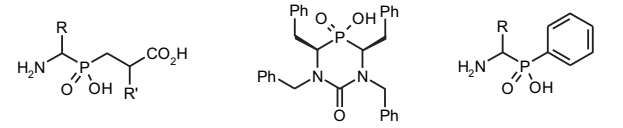
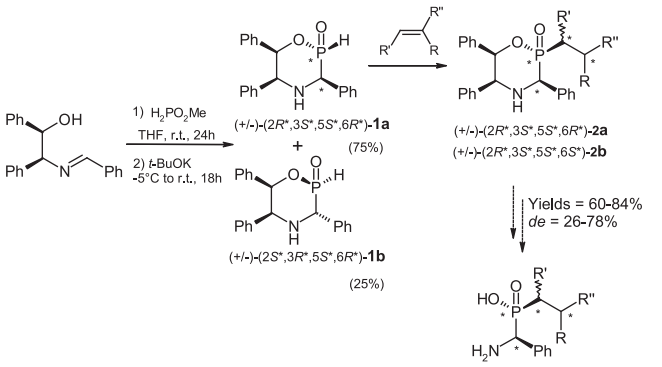



**Fig. 1.** Biologically active phosphinic derivatives.

We described, in previous publications, the synthesis of a new class of phosphorus heterocycles, the 2*H*-2-oxo-1,4,2-oxaza phosphinanes (±)-**1a** and (±)-**1b** bearing a reactive P–H bond and the diastereoselective additions of **1a** to aldehydes or imines, as well as palladium catalysed P-arylations or P-vinylation.[5a–h]

2*H*-2-Oxo-1,4,2-oxaza phosphinanes **1a** and **1b** were synthesised from the addition of methyl hypophosphite to a racemic imino-alcohol followed by an intramolecular transesterification. After the investigation of the reactivity of the major isomer (±)-**1a**, which was isolated by preferential crystallization, in nucleophilic additions on aldehydes and aldimides, we decided to investigate the diastereoselective Michael addition for the preparation of phosphinodipeptide analogs (Scheme 1).




**Scheme 1.** Racemic 2*H*-2-oxo-1,4,2-oxazaphosphinane **1a** for the preparation of phosphinodipeptide analogs.

Compound (±)-**1a** was chosen by the fact that this diastereomer presents the three bulkiest groups on the same side of the reactive P–H bond. Then, it could induce better diastereoselectivity on the P-Michael addition process.

## 2. Results and discussion

According to the previous publications,[5c] the reaction required catalytic amounts of potassium *tert*-butoxide as base for the activation of the nucleophilic phosphorus site. α-Substituted, β-substituted, and cyclic olefins were used in order to investigate the influence of steric hindrance on diastereoselectivity (Scheme 2, Table 1). On this way, the proximity effect of the reactive pro-chiral center conjugated to the bulky groups has been studied, as well as the effect of the substituted olefin and rigid olefins on the Michael diastereoselection addition.

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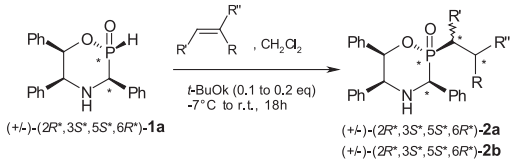



(+/-)-(2R*,3S*,5S*,6R*)-**1a**

(+/-)-(2R*,3S*,5S*,6R*)-**2a**

(+/-)-(2R*,3S*,5S*,6R*)-**2b**

**Scheme 2.** Michael reaction of **1a** to electron deficient olefins.

The corresponding enantiopur imine was easily accessible through the same reaction previously described for the racemic,[5c] via condensation under drying agent ($MgSO_4$) of benzaldehyde on the commercial chiral (−)-(1*R*,2*S*) 2-amino-1,2-diphenylethanol (yield=80% after crystallization). Following, the heterocyclic phosphorus compounds, the 2*H*-2-oxo-1,4,2-oxaza phosphinanes (+)-(2*R*,3*S*,5*S*,6*R*)-**1a** was prepared by a similar way than its racemic form and recovered pure by precipitation with 30% yield (Scheme 4).

**Table 1**
Substitution effects of electron deficient olefins on diastereoselectivity of Michael reaction with **1a**

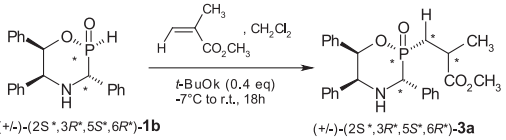
| Entry | R | R′ | R″ | Compounds (±)-(2*R**,3*S**,5*S**,6*R**)-**2a** and -**2b** ($\delta$ $^{31}$P NMR, $CDCl_3$) | Yield | Isolated Yield | de |
|---|---|---|---|---|---|---|---|
| 1 | Me | H | $CO_2Me$ | **2.1a** (50.7), **2.1b** (50.2) | 98 | 75 | 26 |
| 2 | Bn | H | $CO_2Me$ | **2.2a** (50.4), **2.2b** (50.0) | 82 | 60 | 32 |
| 3 | H | Me | $CO_2Me$ | **2.3a** (51.9), **2.3b** (51.8) | 90 | 68 | 54 |
| 4 | H | *i*-Pr | $CO_2Me$ | **2.4a** (54.1), **2.4b** (52.6) | 91 | 60 | 50 |
| 5 | H | Ph | $CO_2Me$ | **2.5a** (48.7), **2.5b** (45.2) | 91 | 70 | 70 |
| 6 | H | Tol | $CO_2Me$ | **2.6a** (49.5), **2.6b** (46.2) | 98 | 70 | 64 |
| 7 | H | Ph | CN | **2.7a** (46.1), **2.7b** (41.9) | 99 | 84 | 70 |
| 8 | Cyclohexenone | | | **2.8a** (48.9), **2.8b** (47.5) | 97 | 76 | 78 |
| 9 | 5,6-Dihydro-2*H*-pyran-2-one | | | **2.9a** (49.3), **2.9b** (46.8) | 94 | 68 | 70 |

First of all, we noticed that reactions occurred in very good to excellent yields (82–99%) and with complete retention of configuration at the phosphorus atom.[6] Indeed, only two diastereomers were obtained which is consistent with the absence of epimerization. New stereogenic centers, respectively, in α- and / or β-position to phosphorus atom can be formed depending on the nature of R and R′ substituents in diastereomeric excess ranging from 26 to 78%. Diastereoselectivity was deeply influenced by the position of substituents on the olefins: whereas α-substituted olefins (entries 1 and 2) gave poor diastereoselectivity with de about 30% even with the larger benzyl group instead of methyl one, β-substituted olefins (entries 3–7) permitted to reach 50% de in aliphatic series (R=Me, *i*-Pr), and up to 70% from methyl (2*E*)-3-phenylacrylate (entry 5). In the same time, cyclic substrates, such as cyclohexenone or lactone (entries 8 and 9) gave, respectively, de equals to 78% and 70%, clearly confirming that the restricted conformation has significant impact on diastereoselectivity. Furthermore, we noticed that for acrylonitrile (entry 7), diastereoselectivity was comparable to the ester.

Concomitantly with the formation of **2.1**, two more compounds ($^{31}$P NMR: $\delta$=46.6 and 46.2 ppm) were formed in 20% yield when using 0.13 equiv of potassium *tert*-butoxide instead of 0.08 equiv showing a high sensitivity of the reaction to the quantity of base. Addition of 0.4 equiv increased the ratio of such compounds. In parallel, we reproduced the reaction starting from the diastereomer (±)-**1b** and methyl methacrylate (Scheme 3). Yield and diastereoselectivity (90%, de=30%) were similar to those observed with (±)-**1a** (97% yield, de=26%) and afforded diastereomeric adducts **3a** and **3b**. Then, mixing the two reaction mixtures showed that side products formed from (±)-**1a** corresponded to **3a** and **3b** clearly demonstrating a double epimerisation both at carbon and phosphorus atom.

## 2.1. Synthesis of enantiopur oxazaphosphinanes

The study was done to quantify the diastereoselectivity with the enantiopur oxazaphosphinane (+)-(2*R*,3*S*,5*S*,6*R*)-**1a** instead of the racemic.

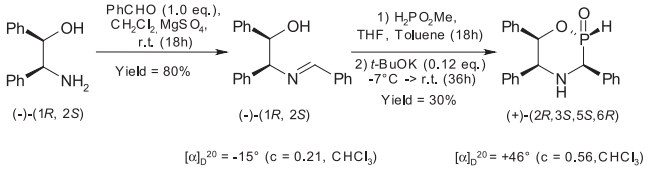



(+/-)-(2S*,3R*,5S*,6R*)-**1b**

(+/-)-(2S*,3R*,5S*,6R*)-**3a**

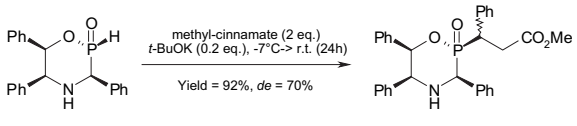
(+/-)-(2S*,3R*,5S*,6R*)-**3b**

**Scheme 3.** Michael addition of **1b** to α-methyl methacrylate.




**Scheme 4.** Synthesis of the enantiopure oxazaphosphinane (+)-(2*R*,3*S*,5*S*,6*R*)-**1a**.

The addition was made as described for the racemic compound and led to a mixture of two diastereomers in 85/15 ratio (Scheme 5). The major stereoisomer was isolated after column chromatography on silica gel. The diastereoisomeric excess obtained during the Michael additions with (+)-(2*R*,3*S*,5*S*,6*R*)-**1a** was identical to the racemic series (Table 2).




(+)-(2R,3S,5S,6R)-**1a**

(-)-**2.5a**, **2.5b**

**Scheme 5.** Michael addition on the enantiopure methyl cinnamate (+)-(2*R*,3*S*,5*S*,6*R*)-**2.5**.

**Table 2**
Comparison of the additions for (+)-(2*R*,3*S*,5*S*,6*R*)-**1a** and (±)-*ulu*-**1a**

| 2-*H*-[1,4,2]Oxazaphosphinane | NMR yield (%) | de (ratio) |
|---|---|---|
| (±)-(2*R**,3*S**,5*S**,6*R**)-**1a** | 99 | 70% (85/15) |
| (+)-(2*R*,3*S*,5*S*,6*R*)-**1a** | 92 | 70% (85/15) |

## 3. Conclusion

In conclusion, we demonstrated the good reactivity of either racemic or enantiopur 2*H*-[1,4,2]-oxazaphosphinane as a nucleophile reagent in Michael addition to olefins activated by electron withdrawing group (isolated yield >60%). Besides, we were able to demonstrate its efficiency as asymmetric inductor for chiral center newly created. This diastereoselectivity showed the interest of the cyclic oxazaphosphinane structure during diastereoselective Michael additions on racemic or enantiopur oxazaphosphinane.

## 4. Experimental

### 4.1. General

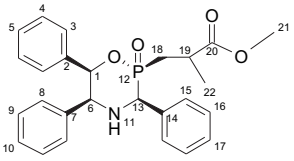
All reactions were carried out under nitrogen atmosphere using Schlenk techniques. The solvents were dried using standard

methods, distilled, and stored under nitrogen. Reactions were monitored by $^{31}P$ NMR using DMSO-$d_6$ as internal references. Column chromatographies were performed on silica gel (Merck 60 AC. 35–70 μm).

$^{31}P$, $^{1}H$, and $^{13}C$ NMR spectra were recorded on BRUKER AVANCE 250 and BRUKER AC-200 spectrometers. MS and HRMS were recorded on a JEOL JMS DX-300 using NBA as matrix in $FAB^+$ ionization mode. IR spectra were measured on a Perkin–Elmer 377 spectrometer.

### 4.2. General procedure

At −5 °C, under $N_2$ and in a 20 mL flask containing 600 mg of (±)-**1a** (1.72 mmol, 1 equiv), are added successively 14 mL of dichloromethane, 200 μL of methyl methacrylate (1.89 mmol, 1.1 equiv), and 230 μL of a solution of *t*-BuOK in THF (0.6 M, 0.14 mmol, 0.08 equiv). Under stirring, the solution returned slowly to ambient temperature. A yellow tint appeared some minutes after addition of the base. At the end of the process two widely major compounds were obtained ($\delta$ $^{31}P$: **2.1a** 50.33 and **2.1b** 50.77 ppm) with a ratio of 37/63 and 26% de. After addition of water until reaching pH=7, extraction with dichloromethane, drying over $Na_2SO_4$, and evaporation of solvents under vacuum, a white solid was recovered. Further, purification by column chromatography on silica (hexane/ethyl acetate gradient: 70/30 to 0/100) gave a final white solid containing two diastereoisomers (580 mg, 75% yield).

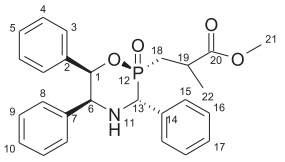


*4.2.1. (2R*,3S*,5S*,6R*)-(±)-2-Methyl-3-(2-oxo-3,5,6-triphenyl-2λ*5*-[1,4,2]oxazaphosphinan-2-yl)-methyl propionate.* de=26%.

Compound **2.1a**: $^{31}P$ NMR (81.02 MHz, $CDCl_3$): $\delta$ 50.65; $^{1}H$ NMR (200.13 MHz, $CDCl_3$): $\delta$ 1.20 (d, 3H, $^{3}J_{HH}$=7.1 Hz, $^{22}CH_3CHCH_2$), 1.83 (m, 1H, $P^{18a}CH_2CH$), 2.19 (m, 1H, $P^{18b}CH_2CH$), 2.44 (m, 1H, $CH_3{}^{19}CHCH_2$), 2.28 (d, 1H, $^{3}J_{PH}$=29.4 Hz, $^{11}NH$), 3.60 (s, 3H, $CO_2{}^{21}CH_3$), 4.88 (m, 1H, $N^6CHPh$), 4.92 (d, 1H, $^{2}J_{PH}$=14.1 Hz, $P^{13}CHN$), 5.90 (dd, 1H, $^{3}J_{HH}$=5.4 Hz, $^{3}J_{PH}$=8.4 Hz, $O^1CHPh$), 7.1–7.7 (m, 15H, *CHar*); $^{13}C$ NMR (50.32 MHz, $CDCl_3$): $\delta$ 19.15 (d, $^{3}J_{PC}$=4.8 Hz, $^{22}CH_3CHCH_2$), 27.95 (d, $^{1}J_{PC}$=96.5 Hz, $P^{18}CH_2CH$), 33.61 (d, $^{2}J_{PC}$=2.9 Hz, $CH_3{}^{19}CHCH_2$), 52.37 (s, $CO_2{}^{21}CH_3$), 62.36 (d, $^{1}J_{PC}$=92.9 Hz, $P^{13}CHN$), 63.94 (d, $^{3}J_{PC}$=1.4 Hz, $N^6CHPh$), 79.24 (d, $^{2}J_{PC}$=7.0 Hz, $O^1CHPh$), 127.14–129.59 (m, *C*Har), 135.46 (d, $^{2}J_{PC}$=5.5 Hz, $^{14}$CarCHP), 136.57 (d, $^{3}J_{PC}$=6.5 Hz, $^{2}$CarCHO), 139.07 (s, $^{7}$CarCHN), 176.23 (d, $^{3}J_{PC}$=14.4 Hz, $^{20}CO_2CH_3$).

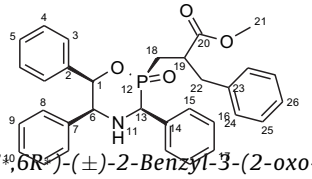
Compound **2.1b**: $^{31}P$ NMR (81.0 MHz, $CDCl_3$): 50.19; $^{1}H$ NMR (200.13 MHz, $CDCl_3$): $\delta$ 1.08 (d, 3H, $^{3}J_{HH}$=7.1 Hz, $^{22}CH_3CHCH_2$), 1.53 (m, 1H, $P^{18a}CH_2CH$), 2.44 (m, 1H, $P^{18b}CH_2CH$), 2.66 (m, 1H, $CH_3{}^{19}CHCH_2$), 2.28 (d, 1H, $^{3}J_{PH}$=29.4 Hz, $^{11}NH$), 3.63 (s, 3H, $CO_2{}^{21}CH_3$), 4.77 (m, 1H, $N^6CHPh$), 4.92 (d, 1H, $^{2}J_{PH}$=14.1 Hz, $P^{13}CHN$), 5.90 (dd, 1H, $^{3}J_{HH}$=5.4 Hz, $^{3}J_{PH}$=8.4 Hz , $O^1CHPh$), 7.1–7.7 (m, 15H, *CHar*); $^{13}C$ NMR (50.32 MHz, $CDCl_3$): $\delta$ 19.38 (d, $^{3}J_{PC}$=8.64 Hz, $^{22}CH_3CHCH_2$), 28.13 (d, $^{1}J_{PC}$=96.0 Hz, $P^{18}CH_2CH$), 33.62 (d, $^{2}J_{PC}$=3.8 Hz, $CH_3{}^{19}CHCH_2$), 52.40 (s, $CO_2{}^{21}CH_3$), 62.00 (d, $^{1}J_{PC}$=92.9 Hz, $P^{13}CHN$), 64.07 (d, $^{3}J_{PC}$=1.0 Hz, $N^6CHPh$), 79.05 (d, $^{2}J_{PC}$=7.0 Hz, $O^1CHPh$), 127.14–129.59 (m, *C*Har), 135.34 (d, $^{2}J_{PC}$=5.3 Hz, $^{14}$CarCHP), 136.55 (d, $^{3}J_{PC}$=6.5 Hz, $^{2}$*Car*CHO), 139.11 (s, $^{7}$CarCHN), 176.28 (d, $^{3}J_{PC}$=10.1 Hz, $^{20}CO_2CH_3$).

IR (KBr): 3440, 3270, 3080, 3050, 3020, 2950, 2870, 1730, 1600, 1490, 1450, 1430, 1230.1210, 1190, 1160, 1180, 1120, 1080, 1060, 1030, 990, 950, 810, 760, 700 $cm^{-1}$; HRMS *m*/*z* ($MH^+$) 450.1834 (calcd for $C_{26}H_{28}NO_4P$: 450.1830).



*4.2.2. (2S*,3R*,5R*,6S*)-(±)-2-Methyl-3-(2-oxo-3,5,6-triphenyl-2λ*5*-[1,4,2]oxazaphosphinan-2-yl)-methyl propionate.* de=26%.

Starting from 530 mg of (±)-**1b** (1.52 mmol, 1 equiv) and 243 μL of methyl methacrylate (2.28 mmol, 1.5 equiv) followed by 506 μL of a solution of *t*-BuOK (0.6 M) in THF (0.3 mmol, 0.2 equiv). The crude material recovered was purified by column chromatography (hexane/ethyl acetate gradient: 30/70 to 0/100) to give a white solid containing two diastereoisomers (512 mg, yield 75%).



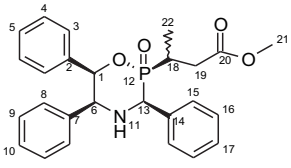
*4.2.3. (2R*,3S*,5S*,6R*)-(±)-2-Benzyl-3-(2-oxo-3,5,6-triphenyl-2λ*5*-[1,4,2]oxazaphosphinan-2-yl)-methyl propionate.* de=32%.

Starting from 556 mg of (±)-**1a** (1.59 mmol, 1 equiv) and 350 μL of α-benzyl methacrylate followed by 265 μL of a solution of *t*-BuOK (0.6 M) in THF (0.16 mmol, 0.1 equiv). 1.20 g was purified by column chromatography (hexane/ethyl acetate gradient: 50/50 to 40/60). White solid (501 mg); $R_f$=0.14 (Hex/AcOEt: 50/50); two diastereoisomers. Yield 60%.

Compound **2.2a**: $^{31}P$ NMR (101.25 MHz, $CDCl_3$): $\delta$ 50.4; $^{1}H$ NMR (250.13 MHz, $CDCl_3$): $\delta$ 1.02–2.85 (m, 6H, $^{11}NH$, $CH^{18}CHP$, $CH^{19}CH_2CO_2CH_3$, $Ph^{22}CH_2CH$), 3.48 (s, 3H, $CO_2{}^{21}CH_3$), 4.76 (d, 1H, $^{3}J_{HH}$=5.3 Hz, $N^6CHPh$), 4.88 (d, 1H, $^{2}J_{PH}$=14.1 Hz, $P^{13}CHPh$), 5.85 (dd, 1H, $^{3}J_{HH}$=5.5 Hz, $^{3}J_{PH}$=7.8 Hz, $O^1CHPh$), 6.97–7.60 (m, 20H, *CHar*); $^{13}C$ NMR (62.90 MHz, $CDCl_3$): $\delta$ 26.23 (d, $^{1}J_{PC}$=96.4 Hz, $P^{18}CH_2CH$), 39.45 (d, $^{2}J_{PC}$=8.2 Hz, $CH_2{}^{19}CHCO_2CH_3$), 40.92 (d, $^{2}J_{PC}$=3.4 Hz, $Ph^{22}CH_2CH$), 52.16 (s, $CO_2{}^{21}CH_3$), 62.74 (d, $^{3}J_{PC}$=93.1 Hz, $P^{13}CHPh$), 63.91 (d, $^{3}J_{PC}$=1.4 Hz, $N^6CHPh$), 79.40 (d, $^{2}J_{PC}$=6.7 Hz, $O^1CHPh$), 127.09–129.72 (m, *C*Har), 135.54 (d, $^{2}J_{PC}$=5.3 Hz, $^{14}$CarCH[(P)(NH)]), 136.61 (d, $^{3}J_{PC}$=6.2 Hz, $^{2}$CarCHO), 138.45 (s, $^{23}CarCH_2$), 139.01 (s, $^{7}$CarCHN), 174.82 (d, $^{3}J_{PC}$=10.1 Hz, $^{20}CO_2CH_3$).

Compound **2.2b**: $^{31}P$ NMR (101.25 MHz, $CDCl_3$): $\delta$ 50.0; $^{1}H$ NMR (250.13 MHz, $CDCl_3$): $\delta$ 1.02–2.85 (m, 6H, $^{11}NH$, $CH^{18}CHP$, $CH^{19}CH_2CO_2CH_3$, $Ph^{22}CH_2CH$), 3.43 (s, 3H, $CO_2{}^{21}CH_3$), 4.73 (d, 1H, $^{3}J_{HH}$=7.4 Hz, $N^6CHPh$), 4.88 (d, 1H, $^{2}J_{PH}$=14.1 Hz, $P^{13}CHPh$), 5.85 (dd, 1H, $^{3}J_{HH}$=5.5 Hz, $^{3}J_{PH}$=7.8 Hz, $O^1CHPh$), 6.97–7.60 (m, 20H, *CHar*); $^{13}C$ NMR (62.90 MHz, $CDCl_3$): $\delta$ 26.84 (d, $^{1}J_{PC}$=96.0 Hz, $P^{18}CH_2CH$), 40.38 (d, $^{2}J_{PC}$=11.5 Hz, $CH_2{}^{19}CHCO_2CH_3$), 41.19 (d, $^{2}J_{PC}$=3.4 Hz, $Ph^{22}CH_2CH$), 52.08 (s, $CO_2{}^{21}CH_3$), 61.91 (d, $^{3}J_{PC}$=92.1 Hz, $P^{13}CHPh$), 63.98 (s, $N^6CHPh$), 79.08 (d, $^{2}J_{PC}$=7.2 Hz, $O^1CHPh$), 127.09–129.72 (m, *C*Har), 135.33 (d, $^{2}J_{PC}$=5.3 Hz, $^{14}$CarCH[(P).(NH)]), 136.56 (d, $^{3}J_{PC}$=6.2 Hz, $^{2}$CarCHO), 138.24 (s, $^{23}CarCH_2$), 139.12 (s, $^{7}$CarCHN), 175.04 (d, $^{3}J_{PC}$=6.2 Hz, $^{20}CO_2CH_3$).

IR (KBr): 3440, 3430, 3280, 3080, 3050, 3020, 2940, 2850, 1730, 1600, 1490, 1450, 1430, 1230, 1175, 1080, 950, 700 $cm^{-1}$; HRMS *m*/*z* ($MH^+$) 526.2147 (calcd for $C_{26}H_{28}NO_4P$: 523.2180).



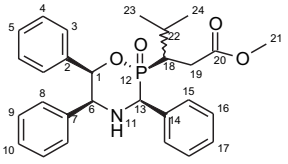
*4.2.4. (2R*,3S*,5S*,6R*)-(±)-3-(2-Oxo-3,5,6-triphenyl-2λ*5*-[1,4,2] oxazaphosphinan-2-yl)-methyl butyrate.* de=54%.

Starting from 469 mg of (±)-**1a** (1.34 mmol, 1 equiv) and 185 μL of methyl crotonate (1.75 mmol, 1.3 equiv) followed by 560 μL of a solution of *t*-BuOK (0.6 M) in THF (0.33 mmol, 0.25 equiv). 543 mg was purified by column chromatography (hexane/ethyl acetate gradient: 45/55 to 0/100). White solid (410 mg); two diastereoisomers. Yield 68%.

Compound **2.3a**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): δ 51.77; $^{1}$H NMR (250.13 MHz, $CDCl_3$): δ 1.22 (dd, 3H, $^{3}J_{HH}$=7.1 Hz, $^{3}J_{PH}$=15.6 Hz, $^{22}CH_3CH$), 1.64 (ddd, 1H, $^{3}J_{HH}$=9.9 Hz, $^{3}J_{PH}$=1.4 Hz, $^{2}J_{HH}$=16.5 Hz, $CH^{19}CH_2CO_2CH_3$), 2.11 (ddd, 1H, $^{3}J_{HH}$=4.3 Hz, $^{3}J_{PH}$=11.3 Hz, $^{2}J_{HH}$=16.8 Hz, $CH^{19}CH_2CO_2CH_3$), 2.72 (m, 1H, $P^{18}CHCH_3$), 3.60 (s, 3H, $CO_2{}^{21}CH_3$), 4.67 (d, 1H, $^{3}J_{HH}$=5.2 Hz, $N^{6}CHPh$), 5.01 (d, 1H, $^{2}J_{HH}$=13.6 Hz, $P^{13}CHPh$), 5.95 (dd, 1H, $^{3}J_{HH}$=5.5 Hz, $^{3}J_{PH}$=7.6 Hz, $O^{1}CHPh$), 7.05–7.75 (m, 15H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): δ 13.40 (d, $^{2}J_{PC}$=6.2 Hz, $^{22}CH_3CH$), 26.44 (d, $^{1}J_{PC}$=96.9 Hz, $P^{18}CHCH_3$), 34.85 (s, $CH^{19}CH_2CO_2CH_3$), 52.05 (s, $CO_2{}^{21}CH_3$),61.95 (d, $^{2}J_{PC}$=90.2 Hz, $P^{13}CHPh$), 63.99 (s, $N^{6}CHPh$), 78.60 (d, $^{2}J_{PC}$=6.7 Hz, $O^{1}CHPh$), 125.61–130.06 (m, *C*Har), 135.18 (d, $^{2}J_{PC}$=6.2 Hz, $^{14}$CarCHP), 136.74 (d, $^{3}J_{PC}$=6.2 Hz, $^{2}$CarCHO), 139.18 (s, $^{7}$CarCHN), 172.40 (d, $^{3}J_{PC}$=20.2 Hz, $^{20}CO_2CH_3$).

Compound **2.3b**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): δ 51.86; $^{1}$H NMR (250.13 MHz, $CDCl_3$): δ 0.61 (dd, 3H, $^{3}J_{HH}$=7 Hz, $^{3}J_{PH}$=17.4 Hz, $^{22}CH_3CH$), 2.28 (ddd, 1H, $^{3}J_{HH}$=9.9 Hz, $^{3}J_{PH}$=7.2 Hz, $^{2}J_{HH}$=16.8 Hz, $CH^{19}CH_2CO_2CH_3$), 2.72 (m, 1H, $P^{18}CHCH_3$), 2.92 (ddd, 1H, $^{3}J_{HH}$=10.0 Hz, $^{3}J_{PH}$=3.2 Hz, $^{2}J_{HH}$=16.0 Hz, $CH^{19}CH_2CO_2CH_3$), 3.66 (s, 3H, $CO_2{}^{21}CH_3$), 4.80 (d, 1H, $^{3}J_{HH}$=4.1 Hz, $N^{6}CHPh$), 4.98 (d, 1H, $^{2}J_{PH}$=13.8 Hz, $P^{13}CHPh$), 5.93 (dd, 1H, $^{3}J_{HH}$=5.3 Hz, $^{3}J_{PH}$=5.3 Hz, $O^{1}CHPh$), 7.05–7.75 (m, 5H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): δ 14.16 (d, $^{2}J_{PC}$=3.4 Hz, $^{22}CH_3CH$), 26.96 (d, $^{1}J_{PC}$=94.5 Hz, $P^{18}CHCH_3$), 34.62 (d, $^{2}J_{PC}$=2.9 Hz, $CH^{19}CH_2CO_2CH_3$), 52.19 (s, $CO_2{}^{21}CH_3$), 62.44 (d, $^{2}J_{PC}$=89.7 Hz, $P^{13}CHPh$), 64.05 (s, $N^{6}CHPh$), 78.95 (d, $^{2}J_{PC}$=6.7 Hz, $O^{1}CHPh$), 125.61–130.06 (m, *C*Har), 135.27 (d, $^{2}J_{PC}$=6.7 Hz, $^{14}$CarCHP), 136.69 (d, $^{3}J_{PC}$=6.7 Hz, $^{2}$CarCHO), 139.07 (s, $^{7}$CarCHN), 172.62 (d, $^{3}J_{PC}$=15.8 Hz, $^{20}CO_2CH_3$).

IR (KBr): 3450, 3290, 3080, 3060, 3030, 2950, 2870, 1735, 1490, 1450, 1430, 1230, 1185, 955, 700 $cm^{-1}$; HRMS *m*/*z* ($MH^+$) 450.1834 (calcd for $C_{26}H_{28}NO_4P$: 450.1833); MS FAB(+) 284 (98%),180 (70%),106 (10%).



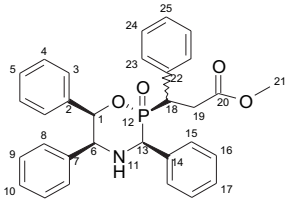
*4.2.5. (2R*,3S*,5S*,6R*)-(±)-3-(2-Oxo-3,5,6-triphenyl-2λ*5*-[1,4,2] oxazaphosphinan-2-yl)-4-methyl-methyl pentanoate.* de=50%.

Starting from 491 mg of (±)-**1a** (1.41 mmol, 1 equiv) and 263 μL of 4-methylpent-2-enoate (1.82 mmol, 1.3 equiv) followed by 583 μL of a solution of *t*-BuOK (0.6 M) in THF (0.35 mmol, 0.25 equiv). 550 mg was purified by column chromatography (hexane/ethyl acetate gradient: 40/60 to 20/80). White solid (404 mg); two diastereoisomers. Yield 60%.

Compound **2.4a**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): δ 54.13; $^{1}$H NMR (250.13 MHz, $CDCl_3$): δ 0.84 (d, 3H, $^{3}J_{HH}$=6.8 Hz, $^{23}CH_3CH$), 1.07 (d, 3H, $^{3}J_{HH}$=6.9 Hz, $^{24}CH_3CH$), 1.74 (ddd, 1H, $^{3}J_{HH}$=2.9 Hz, $^{3}J_{PH}$=15.0 Hz, $^{2}J_{HH}$=18.0 Hz, $CH^{19}CH_2CO_2CH_3$), 2.21 (ddd, 1H , $^{3}J_{HH}$=9.0 Hz, $^{3}J_{PH}$=6.5 Hz, $^{2}J_{HH}$=18.0 Hz, $CH^{19}CH_2CO_2CH_3$), 2.37(m, 1H, $CH^{22}CHCH_3$), 2.82 (dddd, 1H, $^{3}J_{HH}$=2.7 Hz, $^{3}J_{HH}$=2.7 Hz, $^{3}J_{PH}$=15.9 Hz, $^{3}J_{HH}$=8.8 Hz, $CH^{18}CHP$), 3.52 (s, 3H, $CO_2{}^{21}CH_3$), 4.75 (d, 1H, $^{3}J_{HH}$=5.5 Hz, $N^{6}CHPh$), 4.92 (d, 1H, $^{2}J_{PH}$=13.3 Hz, $P^{13}CHPh$), 5.96 (dd, 1H, $^{3}J_{HH}$=5.5 Hz, $^{3}J_{PH}$=8.0 Hz, $O^{1}CHPh$), 7.05–7.75 (m, 15H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): δ 19.77 (d, $^{3}J_{PC}$=1.4 Hz, $^{23}CH_3CH$), 21.50 (d, $^{3}J_{PC}$=13.4 Hz, $^{24}CH_3CH$), 27.90 (d, $^{2}J_{PC}$=4.8 Hz, $CH^{22}CHCH_3$), 28.97 (s, $CH^{19}CH_2CO_2CH_3$), 35.64 (d, $^{1}J_{PC}$=92.6 Hz, $P^{18}CHCH_2$), 52.06 (s, $CO_2{}^{21}CH_3$), 62.26 (d, $^{1}J_{PC}$=89.3 Hz, $P^{13}CHPh$), 63.94 (s, $N^{6}CHPh$), 78.53 (d, $^{2}J_{PC}$=6.7 Hz, $O^{1}CHPh$), 127.17–128.66 (m, *C*Har), 135.24 (d, $^{2}J_{PC}$=4.8 Hz, $^{14}$CarCHP), 136.84 (d, $^{3}J_{PC}$=7.2 Hz, $^{2}$CarCHO), 139.27 (s, $^{7}$CarCHN), 172.93 (d, $^{3}J_{PC}$=17.3 Hz, $^{20}CO_2CH_3$); $R_f$=0.34 (hexane/ethyl acetate: 50/50).

Compound **2.4b**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): δ 52.60; $^{1}$H NMR (250.13 MHz, $CDCl_3$): δ 0.55 (dd, 3H, $^{3}J_{HH}$=6.9 Hz, $^{3}J_{PH}$=1.0 Hz, $^{23}CH_3CH$), 0.92 (d, 3H, $^{3}J_{HH}$=6.6 Hz, $^{24}CH_3CH$), 1.39 (m, 1H, $CH^{22}CHCH_3$), 2.41 (ddd, 1H, $^{3}J_{HH}$=5.9 Hz, $^{3}J_{PH}$=14.3 Hz, $^{2}J_{HH}$=16.6 Hz, $CH^{19}CH_2CO_2CH_3$), 2.86(ddd, 1H, $^{3}J_{HH}$=6.3 Hz, $^{3}J_{PH}$=15.2 Hz, $^{2}J_{HH}$=16.4 Hz, $CH^{19}CH_2CO_2CH_3$), 2.58 (tdd, 1H, $^{3}J_{HH}$=2.0 Hz, $^{3}J_{HH}$=5.9 Hz, $^{3}J_{PH}$=12.9 Hz, $CH^{18}CHP$), 3.57 (s, 3H, $CO_2{}^{21}CH_3$), 4.78 (d, 1H, $^{3}J_{HH}$=5.7 Hz, $N^{6}CHPh$), 4.89 (d, 1H, $^{2}J_{PH}$=13.1 Hz, $P^{13}CHPh$), 5.89 (dd, 1H, $^{3}J_{HH}$=6.2 Hz, $^{3}J_{PH}$=12.3 Hz, $O^{1}CHPh$), 6.96–7.68 (m, 15H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): δ 18.39 (s, $^{23}CH_3CH$), 21.88 (d, $^{3}J_{PC}$=16.3 Hz, $^{24}CH_3CH$), 28.19 (d, $^{2}J_{PC}$=3.4 Hz, $CH^{22}CHCH_3$), 27.16 (s, $CH^{19}CH_2CO_2CH_3$), 36.26 (d, $^{1}J_{PC}$=90.2 Hz, $P^{18}CHCH_2$), 52.19 (s, $CO_2{}^{21}CH_3$), 63.57 (d, $^{1}J_{PC}$=87.8 Hz, $P^{13}CHPh$), 63.74 (s, $N^{6}CHPh$), 77.73 (d, $^{2}J_{PC}$=4.8 Hz, $O^{1}CHPh$), 127.01–129.52 (m, *C*Har), 135.98 (d, $^{2}J_{PC}$=4.8 Hz, $^{14}$CarCHP), 136.99 (d, $^{3}J_{PC}$=7.2 Hz, $^{2}$CarCHO), 139.24 (s, $^{7}$CarCHN), 172.55 (d, $^{3}J_{PC}$=9.6 Hz, $^{20}CO_2CH_3$); $R_f$=0.18 (hexane/ethyl acetate: 50/50).

IR (KBr): 3300, 3060, 3040, 3020, 2960, 2940, 2850, 1735, 1595, 1480, 1450, 1430, 1470, 1380, 1360, 1220, 1185, 1060, 960, 710 $cm^{-1}$; HRMS *m*/*z* ($MH^+$) 478.2147 (calcd for $C_{28}H_{32}NO_4P$: 478.2144); MS FAB(+) 478 (15%), 284 (100%),180 (25%),106 (15%).



*4.2.6. (2R*,3S*,5S*,6R*)-(±)-3-Phenyl-3-(2-oxo-3,5,6-triphenyl-2λ*5*-[1,4,2]oxazaphosphinan-2-yl)-methyl propionate.* de=70%.

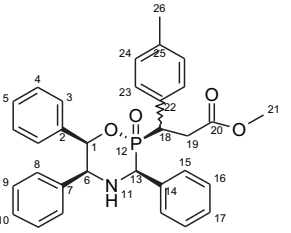
Starting from 500 mg of (±)-**1a** (1.43 mmol, 1 equiv) and 463 mg of methyl cinnamate (2.86 mmol, 2.7 equiv) followed by 239 μL of a solution of *t*-BuOK (0.6 N) in THF (0.14 mmol, 0.1 equiv). The crude material, 1.2 g, was purified by column chromatography (hexane/ethyl acetate gradient: 50/50 to 30/70). White solid (550 mg); two diastereoisomers. Yield 70%.

Compound **2.5a**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): δ 48.67; $^{1}$H NMR (250.13 MHz, $CDCl_3$): δ 1.86 (ddd, 1H, $^{3}J_{HH}$=2.9 Hz, $^{3}J_{PH}$=8.3 Hz, $^{2}J_{HH}$=16.8 Hz, $CH^{19a}CH_2CO_2CH_3$), 2.16 (d, 1H, $^{3}J_{HH}$=5.5 Hz, $^{11}NH$), 2.71 (ddd, 1H, $^{3}J_{HH}$=11.7 Hz, $^{3}J_{PH}$=5.3 Hz, $^{2}J_{HH}$=17.0 Hz, $CH^{19b}CH_2CO_2CH_3$), 3.41 (s, 3H, $CO_2{}^{21}CH_3$), 3.91(ddd, 1H, $^{3}J_{HH}$=2.9 Hz, $^{3}J_{HH}$=11.7 Hz, $^{3}J_{PH}$=12.9 Hz, $CH^{18}CHP$), 4.63 (s, 1H, $N^{6}CHPh$), 5.01 (d, 1H, $^{2}J_{PH}$=12.5 Hz, $P^{13}CHPh$), 5.89 (dd, 1H, $^{3}J_{HH}$=5.7 Hz, $^{3}J_{PH}$=8.0 Hz, $O^{1}CHPh$), 6.65–7.72 (m, 20H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): δ 35.16 (s, $CH^{19}CH_2CO_2CH_3$), 38.18 (d, $^{1}J_{PC}$=91.9 Hz, $P^{18}CHCH_2$), 51.57 (s, $CO_2{}^{21}CH_3$), 60.37 (d, $^{1}J_{PC}$=89.3 Hz, $P^{13}CHPh$), 63.37 (s, $N^{6}CHPh$), 76.89 (d, $^{2}J_{PC}$=6.3 Hz, $O^{1}CHPh$), 126.13–129.58 (m, *C*Har), 134.53 (d, $^{2}J_{PC}$=4.1 Hz, $^{14}$CarCH[(P),(NH)]), 135.41 (d, $^{2}J_{PC}$=8.2 Hz, $^{22}$CarCH[(P),(CH)]), 136.22 (d, $^{3}J_{PC}$=6.7 Hz, $^{2}$CarCHO), 138.76 (s, $^{7}$CarCHN), 171.14 (d, $^{3}J_{PC}$=20.1 Hz, $^{20}CO_2CH_3$); $R_f$=0.32 (hexane/ethyl acetate: 50/50). $[\alpha]_D^{20}$ −146 (*c* 0.2, $CHCl_3$).

Compound **2.5b**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): δ 45.18; $^{1}$H NMR (250.13 MHz, $CDCl_3$): δ 2.15 (ddd, 1H, $^{3}J_{HH}$=10.6 Hz, $^{3}J_{PH}$=7.6 Hz, $^{2}J_{HH}$=16.4 Hz, $CH^{19a}CH_2CO_2CH_3$), 3.23 (ddd, 1H, $^{3}J_{HH}$=4.1 Hz, $^{3}J_{PH}$=9.0 Hz, $^{2}J_{HH}$=16.2 Hz, $CH^{19b}CH_2CO_2CH_3$), 3.42 (s, 3H, $CO_2{}^{21}CH_3$), 3.73 (ddd, 1H, $^{3}J_{HH}$=3.9, 10.6 Hz, $^{3}J_{PH}$=14.3 Hz,

$CH_2{}^{18}CHP$), 4.86 (d, 1H, $^3J_{HH}$=6.0 Hz, $N^6CHPh$), 4.88 (d, 1H, $^2J_{PH}$=12.9 Hz, $P^{13}CHPh$), 5.86 (dd, 1H, $^3J_{HH}$=5.5 Hz, $^3J_{PH}$=5.5 Hz, $O^1CHPh$), 6.92–7.42 (m, 20H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 36.12 (d, $^2J_{PC}$=2.4 Hz, $CH^{19}CH_2CO_2CH_3$), 40.34 (d, $^1J_{PC}$=91.2 Hz, $P^{18}CHCH_2$), 52.12 (s, $CO_2{}^{21}CH_3$), 64.38 (d, $^3J_{PC}$=86.4 Hz, $P^{13}CHPh$), 64.36 (d, $^3J_{PC}$=2.4 Hz, $N^6CHPh$), 79.87 (d, $^2J_{PC}$=7.2 Hz, $O^1CHPh$), 127.09–129.72 (m, *C*Har), 135.05 (d, $^2J_{PC}$=4.1 Hz, $^{14}$CarCH[(P),(NH)]), 135.36 (d, $^2J_{PC}$=3.4 Hz, $^{22}$CarCH[(P),(CH)]), 136.75 (d, $^3J_{PC}$=6.2 Hz, $^2$CarCHO), 138.83 (s, $^7$CarCHN), 171.76 (d, $^3J_{PC}$=15.8 Hz, $^{20}CO_2CH_3$); $R_f$=0.20 (hexane/ethyl acetate: 50/50).

IR (KBr): 3440, 3200, 3090, 3070, 3030, 2950, 2840, 1735, 1600, 1490, 1450, 1430, 1215, 1175, 950, 700 cm$^{-1}$; HRMS *m*/*z* ($MH^+$) 512.1991 (calcd for $C_{31}H_{30}NO_4P$: 512.1978); MS FAB(+) 512 (7%), 284 (43%),180 (12%),106 (24%).



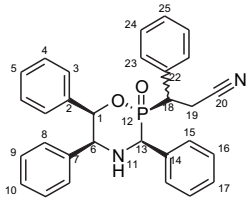
*4.2.7. (2R*,3S*,5S*,6R*)-(±)-3-Tolyl-3-(2-oxo-3,5,6-triphenyl-2λ*5*-[1,4,2]oxazaphosphinan-2-yl)-methyl propionate.* de=64%.

Starting from 502 mg of (±)-**1a** (1.44 mmol, 1 equiv) and 506 mg of methyl cinnamate (2.88 mmol, 2 equiv) followed by 480 μL of a solution of *t*-BuOK (0.6 M) in THF (0.29 mmol, 0.2 equiv). The crude material, 1.2 g, was purified by column chromatography (hexane/ethyl acetate gradient: 30/70 to 0/100). White solid (530 mg); two diastereoisomers. Yield 70%.

Compound **2.6a**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 49.45; $^1$H NMR (250.13 MHz, $CDCl_3$): $\delta$ 1.94 (ddd, 1H, $^3J_{HH}$=2.9 Hz, $^3J_{PH}$=8.4 Hz, $^2J_{HH}$=16.9 Hz, $^{19a}CH_2$), 2.16 (ddd, 1H, $^3J_{HH}$=6.2, 3.2 Hz, $^3J_{PH}$=26.2 Hz, $^{11}NH$), 2.68 (s, 3H, $^{26}CH_3$), 2.74 (ddd, 1H, $^3J_{HH}$=11.5 Hz, $^3J_{PH}$=5.4 Hz, $^2J_{HH}$=16.9 Hz, $^{19b}CH_2$), 3.45 (s, 3H, $CO_2{}^{21}CH_3$), 3.91 (ddd, 1H, $^3J_{HH}$=2.9 Hz, $^3J_{PH}$=13.0 Hz, $CH_2{}^{18}CHP$), 4.65 (dd, 1H, $^3J_{HH}$=4.4 Hz, $N^6CHPh$), 5.04 (d, 1H, $^2J_{PH}$=12.8 Hz, $P^{13}CHPh$), 5.92 (dd, 1H, $^3J_{HH}$=5.9 Hz, $^3J_{PH}$=7.9 Hz, $O^1CHPh$), 6.74–7.75 (m, 19H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 21.56 (s, $^{26}CH_3$), 35.43 (s, $^{19}CH_2$), 38.15 (d, $^1J_{PC}$=91.7 Hz, $P^{18}CHCH_2$), 52.05 (s, $CO_2{}^{21}CH_3$), 60.64 (d, $^1J_{PC}$=88.8 Hz, $P^{13}CHPh$), 63.82 (s, $N^6CHPh$), 77.20 (d, $^2J_{PC}$=6.2 Hz, $O^1CHPh$), 126.56–129.81 (m, *C*Har), 132.62 (d, $J_{PC}$=8.2 Hz, *C*ar), 135.01 (d, $J_{PC}$=4.3 Hz, *C*ar), 136.72 (d, $J_{PC}$=6.7 Hz, *C*ar), 137.32 (d, $J_{PC}$=2.4 Hz, *C*ar), 139.23 (s, *C*ar), 171.67 (d, $^3J_{PC}$=20.6 Hz, $^{20}CO_2$); $R_f$=0.32 (hexane/ethyl acetate: 50/50).

Compound **2.6b**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 45.18; $^1$H NMR (250.13 MHz, $CDCl_3$): $\delta$ 2.16 (ddd, 1H, $^3J_{HH}$=3.2 Hz, $^3J_{PH}$=6.2 Hz, $^2J_{HH}$=26.2 Hz, $^{11}NH$), 2.34 (s, 3H, $^{26}CH_3$), 2.74 (m, 1H, $^{18a}CH_2$), 3.46 (s, 3H, $CO_2{}^{21}CH_3$), 3.25 (ddd, 1H, $^3J_{HH}$=3.8 Hz, $^3J_{PH}$=9.0 Hz, $^2J_{HH}$=16.1 Hz, $^{18b}CH_2$), 3.74 (ddd, 1H, $^3J_{HH}$=4.1 Hz, $^3J_{HH}$=10.8 Hz, $^2J_{PH}$=13.8 Hz, $CH_2{}^{19}CHP$), 4.88 (dd, 1H, $^3J_{HH}$=3.3 Hz, $N^6CHPh$), 4.92 (dd, 1H, $^2J_{PH}$=15.0 Hz, $^3J_{HH}$=4.0 Hz, $P^{13}CHPh$), 5.90 (dd, 1H, $^3J_{HH}$=5.5 Hz, $^3J_{PH}$=5.7 Hz, $O^1CHPh$), 6.74–7.75 (m, 19H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 21.46 (s, $^{26}CH_3$), 35.97 (s, $^{19}CH_2$), 39.36 (d, $^1J_{PC}$=91.2 Hz, $P^{18}CHCH_2$), 52.13 (s, $CO_2{}^{21}CH_3$), 63.99 (d, $^1J_{PC}$=87.8 Hz, $P^{13}CHPh$), 63.68 (s, $N^6CHPh$), 79.50 (d, $^2J_{PC}$=7.2 Hz, $O^1CHPh$), 126.56–129.81 (m, *C*Har), 132.13 (d, $J_{PC}$=3.8 Hz, *C*ar), 135.13 (d, $J_{PC}$=4.3 Hz, *C*ar), 136.79 (d, $J_{PC}$=8.6 Hz, *C*ar), 137.32 (d, $J_{PC}$=2.4 Hz, *C*ar), 138.91 (s, *C*ar), 171.82 (d, $^3J_{PC}$=16.8 Hz, $^{20}CO_2$); $R_f$=0.20 (hexane/ethyl acetate: 50/50).

IR (KBr): 3280, 3080, 3050, 3020, 2940, 2890, 2800, 1730, 1590, 1480, 1450, 1430, 1230,1210, 1180, 1160, 1110, 1080, 1060, 1030, 1010, 1000, 950, 770, 700 cm$^{-1}$; HRMS *m*/*z* ($MH^+$) 525.2147 (calcd for $C_{32}H_{32}NO_4P$: 525.2135); MS FAB(+) 526 (29%), 348 (57%), 284 (95%), 194 (62%), 180 (72%),106 (30%), 91 (50%).



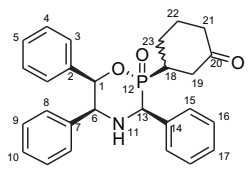
*4.2.8. (2R*,3S*,5S*,6R*)-(±)-3-Phenyl-3-(2-oxo-3,5,6-triphenyl-2λ*5*-[1,4,2]oxazaphosphinan-2-yl) propionitrile.* de=70%.

Starting from 528 mg of (±)-**1a** (1.51 mmol, 1 equiv) and 285 μL of cinnamonitrile (2.27 mmol, 1.5 equiv) followed by 250 μL of a solution of *t*-BuOK (0.6 M) in THF (0.15 mmol, 0.1 equiv). The crude material was purified by column chromatography (hexane/ethyl acetate gradient: 50/50 to 0/100). White solid (530 mg); two diastereoisomers. Yield 84%.

Compound **2.7a**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 46.07; $^1$H NMR (250.13 MHz, $CDCl_3$): $\delta$ 1.55 (ddd, 1H, $^3J_{HH}$=3.2 Hz, $^3J_{PH}$=5.5 Hz, $^2J_{HH}$=17.1 Hz, $CH^{19}CH_2CN$), 2.35 (d, 1H, $^3J_{HH}$=30.7 Hz, $^{11}NH$), 2.68 (ddd, 1H, $^3J_{HH}$=12.5 Hz, $^3J_{PH}$=6.1 Hz, $^2J_{HH}$=17.1 Hz, $CH^{19}CH_2CO_2CH_3$), 3.66 (td, 1H, $^3J_{HH}$=3.2 Hz, $^3J_{HH}$=12.5 Hz, $^3J_{PH}$=12.5 Hz, $CH_2{}^{18}CHP$), 4.68 (d, 1H, $^3J_{HH}$=4.7 Hz, $N^6CHPh$), 5.08 (d, 1H, $^2J_{PH}$=12.1 Hz, $P^{13}CHPh$), 5.92 (dd, 1H, $^3J_{HH}$=5.6 Hz, $^3J_{PH}$=8.6 Hz, $O^1CHPh$), 6.68–7.76 (m, 20H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 20.18 (d, $^2J_{PC}$=3.3 Hz, $CH^{19}CH_2CO_2CH_3$), 38.50 (d, $^1J_{PC}$=91.9 Hz, $P^{18}CHCH_2$), 59.97 (d, $^1J_{PC}$=92.3 Hz, $P^{13}CHPh$), 63.21 (s, $N^6CHPh$), 77.68 (d, $^2J_{PC}$=6.3 Hz, $O^1CHPh$), 117.37 (d, $^3J_{PC}$=22.3 Hz, $CH_2{}^{20}CN$), 125.06–129.85 (m, *C*Har), 133.39 (d, $^2J_{PC}$=7.8 Hz, $^{14}$CarCH[(P),(NH)]), 133.99 (d, $^2J_{PC}$=5.6 Hz, $^{21}$CarCH[(P),($CH_2$)]), 135.68 (d, $^2J_{PC}$=7.4 Hz, $^{22}$CarCH[(P),(CH)]), 138.42 (s, $^7$CarCHN); $R_f$=0.35 (hexane/ethyl acetate: 50/50).

Compound **2.7b**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 42.06; $^1$H NMR (250.13 MHz, $CDCl_3$): $\delta$ 2.83 (ddd, 1H, $^3J_{HH}$=11.9 Hz, $^3J_{PH}$=6.7 Hz, $^2J_{HH}$=16.9 Hz, $CH^{19}CH_2CN$), 2.26 (d, 1H, $^3J_{HH}$=30.0 Hz, $^{11}NH$), 3.16 (ddd, 1H, $^3J_{HH}$=3.7 Hz, $^3J_{PH}$=6.6 Hz, $^2J_{HH}$=17.0 Hz, $CH^{19}CH_2CO_2CH_3$), 3.37 (td, 1H, $^3J_{HH}$=3.7 Hz, $^3J_{HH}$=11.9 Hz, $^3J_{PH}$=13.3 Hz, $CH_2{}^{18}CHP$), 4.95 (d, 1H, $^3J_{HH}$=4.5 Hz, $N^6CHPh$), 4.92 (d, 1H, $^2J_{PH}$=10.9 Hz, $P^{13}CHPh$), 5.88 (dd, 1H, $^3J_{HH}$=5.7 Hz, $^3J_{PH}$=5.7 Hz, $O^1CHPh$), 6.97–7.41 (m, 20H, *C*Har); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 20.67 (d, $^2J_{PC}$=0.7 Hz, $CH^{19}CH_2CO_2CH_3$), 40.29 (d, $^1J_{PC}$=90.4 Hz, $P^{18}CHCH_2$), 64.41 (d, $^1J_{PC}$=91.9 Hz, $P^{13}CHPh$), 63.29 (s, $N^6CHPh$), 80.66 (d, $^2J_{PC}$=7.1 Hz, $O^1CHPh$), 117.34 (d, $^3J_{PC}$=19.4 Hz, $CH_2{}^{20}CN$), 125.06–129.85 (m, *C*Har), 132.95 (d, $^2J_{PC}$=3.0 Hz, $^{14}$CarCH[(P),(NH)]), 133.99 (d, $^2J_{PC}$=5.6 Hz, $^{21}$CarCH[(P),($CH_2$)]), 135.83 (d, $^2J_{PC}$=7.1 Hz, $^{22}$CarCH[(P),(CH)]), 137.90 (s, $^7$CarCHN); $R_f$=0.23 (hexane/ethyl acetate: 50/50).

IR (KBr): 3400, 3280, 3070, 3040, 3010, 2940, 2830, 2790, 2230, 1590, 1480, 1440, 1410, 1230, 1170, 1060, 1080, 950, 700 cm$^{-1}$; HRMS *m*/*z* ($MH^+$) 479.1888 (calcd for $C_{32}H_{32}NO_4P$: 479.1895).



*4.2.9. (2R*,3S*,5S*,6R*)-(±)-3-(2-Oxo-3,5,6-triphenyl-2λ*5*-[1,4,2]oxazaphosphinan-2-yl)-cyclohexanone.* de=78%.

Starting from 528 mg of (±)-**1a** (1.51 mmol, 1 equiv) and 220 μL of 2-cyclohexen-1-one (2.27 mmol, 1.5 equiv) followed by 250 μL of a solution of *t*-BuOK (0.6 M) in THF (0.15 mmol, 0.1 equiv). The crude material was purified by column chromatography (hexane/

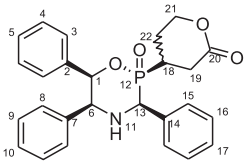
ethyl acetate gradient: 30/70 to 0/100). White solid (511 mg); two diastereoisomers. Yield 76%.

de=78%.

Compound **2.8a**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 48.90; $^{1}$H NMR (250.13 MHz, $CDCl_3$): $\delta$ 0.77–2.61 (m, 10H, P$^{18}$C*H*CH$_2$, $^{19,21,22,23}$C*H*$_2$, and $^{11}$N*H*), 4.72 (d, 1H, $^{3}J_{HH}$=4.9 Hz, N$^{6}$C*H*Ph), 4.96 (d, 1H, $^{2}J_{PH}$=13.3 Hz, P$^{13}$C*H*Ph), 5.91 (dd, 1H, $^{3}J_{HH}$=5.7 Hz, $^{3}J_{PH}$=7.6 Hz, O$^{1}$C*H*Ph), 7.01–7.66 (m, 15H, C*H*ar); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 24.52 (d, $^{3}J_{PC}$=2.7 Hz, CH$_2$$^{22}$*C*H$_2$CH$_2$), 25.79 (d, $^{2}J_{PC}$=17.2 Hz, CH$^{23}$*C*H$_2$CH$_2$), 33.98 (d, $^{1}J_{PC}$=94.3 Hz, P$^{18}$*C*HCH$_2$), 39.33 (d, $^{2}J_{PC}$=5.9 Hz, PC*H*$^{19}$*C*H$_2$), 41.27 (s, CH$_2$$^{21}$*C*H$_2$C=O), 60.96 (d, $^{1}J_{PC}$=91.6 Hz, P$^{13}$C*H*Ph), 63.35 (s, N$^{6}$*C*HPh), 77.93 (d, $^{2}J_{PC}$=6.6 Hz, O$^{1}$CHPh), 126.60–129.33 (m, *C*Har), 134.73 (d, $J_{PC}$=5.5 Hz, *C*ar), 136.09 (d, $J_{PC}$=7.0 Hz, *C*ar), 138.68 (s, *C*ar), 209.15 (d, $^{3}J_{PC}$=13.3 Hz, CH$_2$$^{20}$*C*OCH$_2$).

Compound **2.8b**: $^{31}$P NMR (101.25 MHz, $CDCl_3$) $\delta$ 47.52.

IR (KBr): 3380, 3260, 3080, 3050, 3020, 2940, 2860, 1710, 1600, 1490, 1455, 1420, 1210, 1235, 1190, 1080, 1060, 960, 700 cm$^{-1}$; HRMS *m*/*z* (MH$^{+}$) 446.1885 (calcd for $C_{27}H_{28}NO_3P$: 446.1897).



*4.2.10. (2R*,3S*,5S*,6R*)-(±)-4-(2-Oxo-3,5,6-triphenyl-2λ*5*-[1,4,2] oxazaphosphinan-2-yl)-tetrahydro-pyran-2-one.* de=70%.

Starting from 511 mg of (±)-**1a** (1.46 mmol, 1 equiv) and 189 μL of 5,6-dihydro-2*H*-pyran-2-one (2.20 mmol, 1.5 equiv) followed by 243 μL of a solution of *t*-BuOK (0.6 M) in THF (0.15 mmol, 0.1 equiv). The crude material was purified by column chromatography (hexane/ethyl acetate gradient: 20/80 to 0/100). White (444 mg); two diastereoisomers. Yield 68%.

Compound **2.9a**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 48.32; $^{1}$H NMR (250.13 MHz, $CDCl_3$): $\delta$ 0.86–2.90 (m, 6H, $^{11}$N*H*, $^{18}$*CH*, and $^{22,19}$C*H*$_2$), 3.98 (m, 1H, $^{21a}$C*H*$_2$), 4.18 (m, 1H, $^{21b}$C*H*$_2$), 4.80 (d, 1H, $^{3}J_{HH}$=5.2 Hz, N$^{6}$C*H*Ph), 5.02 (d, 1H, $^{2}J_{PH}$=13.6 Hz, P$^{13}$C*H*Ph), 5.93 (dd, 1H, $^{3}J_{HH}$=5.5 Hz, $^{3}J_{PH}$=7.9 Hz, O$^{1}$C*H*Ph), 7.09–7.71 (m, 15H, C*H*ar); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 22.05 (s, CH$^{22}$*C*H$_2$CH$_2$), 24.63 (d, $^{1}J_{PC}$=131.8 Hz, P$^{18}$CHCH$_2$), 27.49 (d, $^{2}J_{PC}$=7.8 Hz, PCH$^{19}$*C*H$_2$), 66.65 (d, $^{3}J_{PC}$=91.6 Hz, CH$_2$$^{21}$*C*H$_2$O–C=O), 58.14 (d, $^{1}J_{PC}$=127.2 Hz, P$^{13}$*C*HPh), 62.17 (s, N$^{6}$*C*HPh), 76.35 (s, O$^{1}$CHPh), 126.26–128.45 (m, *C*Har), 134.69 (d, $J_{PC}$=7.2 Hz, *C*ar), 136.93 (d, $J_{PC}$=8.8 Hz, *C*ar), 139.75 (s, *C*ar), 169.72 (d, $^{3}J_{PC}$=15.5 Hz, $^{20}$*C*O$_2$). $R_f$=0.39 (Hex/AcOEt: 10/90).

Compound **2.9b**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 46.84.

IR (KBr): 3420, 3260, 3080, 3050, 3020, 2970, 2850, 1740, 1595, 1490, 1450, 1400, 1240, 1225, 1210, 1185, 1080, 950, 700 cm$^{-1}$; HRMS *m*/*z* (MH$^{+}$) 448.1678 (calcd for $C_{26}H_{26}NO_4P$: 448.1663); MS FAB(+) 448 [M+H]$^{+}$ (15%); 284 (100%); 180 (45%); 106 (24%); 91 (22%).

Compound **3.a**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 46.64; $^{1}$H NMR (250.13 MHz, $CDCl_3$): $\delta$ 1.27 (d, 3H, $^{3}J_{HH}$=7.1 Hz, $^{22}$C*H*$_3$CHCH$_2$), 2.20 (dd, 1H, $^{3}J_{PH}$=2.7 Hz, $^{2}J_{HH}$=10.9 Hz, P$^{18a}$C*H*$_2$CH), 2.23 (d, 1H, $^{2}J_{HH}$=11.2 Hz, P$^{18b}$C*H*$_2$CH), 2.56 (m, 1H, CH$_3$$^{19}$*C*HCH$_2$), 2.43 (s large, 1H, $^{11}$N*H*), 3.57 (s, 3H, CO$_2$$^{21}$C*H*$_3$), 4.67 (d, $^{3}J_{HH}$=2.7 Hz, 1H, N$^{6}$C*H*Ph), 4.43 (d, 1H, $^{2}J_{PH}$=17.4 Hz, P$^{13}$C*H*N), 6.01 (s large, 1H, O$^{1}$C*H*Ph), 7.1–7.6 (m, 15H, C*H*ar); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 18.64 (d, $^{3}J_{PC}$=3.8 Hz, $^{22}$*C*H$_3$CHCH$_2$), 23.25 (d, $^{1}J_{PC}$=86.9 Hz, P$^{18}$CH$_2$CH), 33.38 (d, $^{2}J_{PC}$=3.4 Hz, CH$_3$$^{19}$CHCH$_2$), 52.38 (s, CO$_2$$^{21}$CH$_3$), 56.56 (d, $^{1}J_{PC}$=95.0 Hz, P$^{13}$CHN), 62.36 (s, N$^{6}$CHPh), 83.33 (d, $^{2}J_{PC}$=7.7 Hz, O$^{1}$CHPh), 125.61–130.06 (m, *C*Har), 134.99 (d, $J_{PC}$=6.2 Hz, *C*ar), 137.56 (d, $J_{PC}$=6.7 Hz, *C*ar), 136.63 (s, *C*ar), 176.18 (d, $^{3}J_{PC}$=14.4 Hz, $^{20}$*C*O$_2$CH$_3$).

Compound **3.b**: $^{31}$P NMR (101.25 MHz, $CDCl_3$): $\delta$ 46.15; $^{1}$H NMR (250.13 MHz, $CDCl_3$): $\delta$ 1.14 (d, 3H, $^{3}J_{HH}$=6.5 Hz, $^{22}$C*H*$_3$CHCH$_2$), 1.40 (m, 2H, P$^{18}$C*H*$_2$CH), 2.85 (m, 1H, CH$_3$$^{19}$*C*HCH$_2$), 2.83 (s large, 1H, $^{11}$N*H*), 3.77 (s, 3H, CO$_2$$^{21}$C*H*$_3$), 4.77 (d, 1H, $^{3}J_{HH}$=2.7 Hz, N$^{6}$C*H*Ph), 4.62 (d, 1H, $^{2}J_{PH}$=17.4 Hz, P$^{13}$C*H*N), 6.01 (s large, 1H, O$^{1}$C*H*Ph), 7.1–7.7 (m, 15H, C*Har*); $^{13}$C NMR (62.90 MHz, $CDCl_3$): $\delta$ 20.19 (d, $^{3}J_{PC}$=10.6 Hz, $^{22}$CH$_3$CHCH$_2$), 24.11 (d, $^{1}J_{PC}$=86.9 Hz, P$^{18}$*C*H$_2$CH), 32.72 (d, $^{2}J_{PC}$=4.8 Hz, CH$_3$$^{19}$*C*HCH$_2$), 52.32 (s, CO$_2$$^{21}$CH$_3$), 56.36 (d, $^{1}J_{PC}$=94.5 Hz, P$^{13}$CHN), 62.39 (s, N$^{6}$CHPh), 83.44 (d, $^{2}J_{PC}$=7.7 Hz, O$^{1}$CHPh), 127.14–129.59 (m, *C*Har), 134.99 (d, $J_{PC}$=6.2 Hz, *C*ar), 137.77 (d, $J_{PC}$=6.7 Hz, *C*ar), 136.75 (s, *C*ar), 176.53 (d, $^{3}J_{PC}$=6.2 Hz, $^{20}$*C*O$_2$CH$_3$).

HRMS *m*/*z* (MH$^{+}$) 450.1834 (calcd for $C_{26}H_{28}NO_4P$: 450.1836); MS FAB(+) 284 (98%), 180 (70%), 106 (10%).

## Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.10.078.

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