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Pallado-catalysed *P*-arylations and *P*-vinylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes

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Abstract—A simple and effective preparation of 2-aryl- (or 2-vinyl)-1,4,2-oxazaphosphinanes, phosphorus analogues of aryl-morpholinols has been developed, involving palladium catalysed coupling of aryl (or vinyl)-halides with 2-*H*-1,4,2-oxazaphosphinane in presence of triethylamine. A deprotection step was also proposed to afford the corresponding *P*-aryl-α-aminobenzylphosphinic acid.

1. Introduction

Among various organophosphorus compounds synthesized during the last decades, α-aminophosphinic derivatives have shown interesting biological properties especially as enzyme inhibitors: leucine aminopeptidase[1a] or isoaspartyl/β-aspartyl zinc peptidase (**A**),[1b] HIV-1 protease (**B**).[1c–g] On the other hand, arylphosphinic acid derivatives are also known as agents of treating hypercholesterolemia or atherosclerosis (**C**)[1h] or as microsomal aminopeptidase[1i] and thrombin inhibitors (**D**) (Fig. 1).[1j]

As a part of our ongoing efforts in discovery and synthesis of new potent organophosphorus inhibitors (virucide, plant regulators…), the challenge in synthesis of phosphorus containing heterocycle was particularly stimulating. Indeed, it is well known that heterocyclic compounds received much attention of chemists due to their pharmaceutical importance and extensive application in organic synthesis.[2]

In previous works, we described the synthesis of a new class of 1,4,2-oxazaphosphinanes **1** bearing a reactive P–H bond, and the diastereoselective additions of **1** to aldehydes and imines.[3a,b] Arylation of such structure would lead to compounds **2**, phosphorus heterocycles analogues of morpholinols derivatives **3**, widely described for their antidepressing activities (Fig. 2).[4]

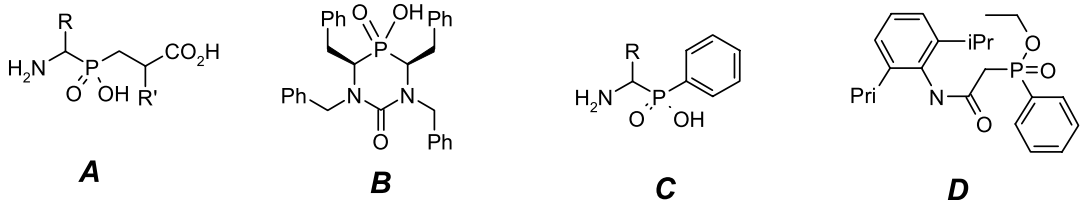

Figure 1. Various biologically active phosphinic derivatives.

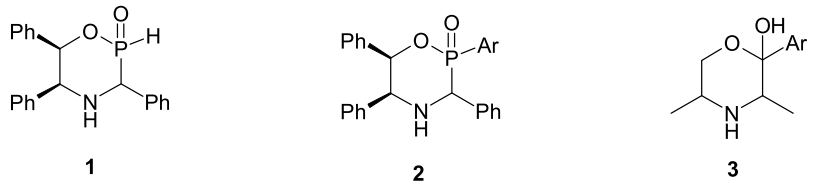

Figure 2. Analogy between *P*-aryl1,4,2-oxazaphosphinanes and aryl-morpholinols.

Keywords: Arylphosphinate; Aminoalkylarylphosphinic acid; Vinylation; Arylation; Pallado-catalyse.
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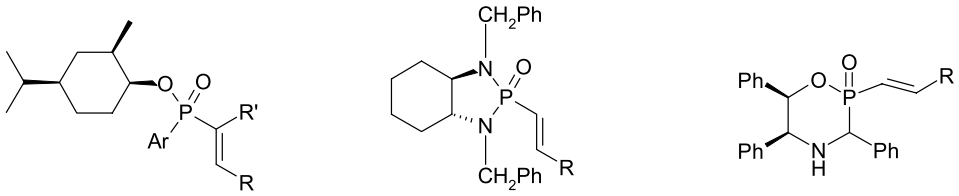


Figure 3. Chiral phosphonic and phosphinic Michael-type olefins.

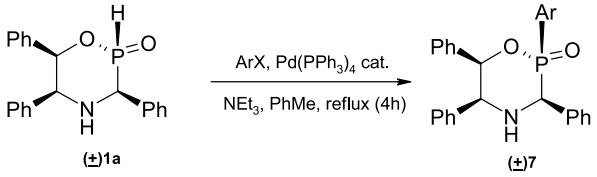
In addition, vinylphosphoryl derivatives[5] **4** and **5** (Fig. 3) were developed to induce diastereoselective additions on the C=C double bond, as the intracyclic phosphorus atoms of these activated olefins is substituted by a chiral group. Vinylation of structure **1** could also give efficient derivatives **6** for diastereoselective reactions.[6]

To the best of our knowledge, only few papers deal with 1,4,2-oxazaphosphinane structures. One of them describes the synthesis of a 2-phenyl-1,4,2-oxazaphosphinane ring starting with chlorophosphines, aminophenol and various substituted aldehydes.[7] We propose herein a different approach via a direct pallado-catalysed arylation or vinylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane **1** affording *P*-aryl- or *P*-vinyl-oxazaphosphinanes.

2. Results and discussion

2.1. Arylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane 1a

Diastereoisomer **1a** was chosen as substrate for arylation and vinylation reactions as its relative stereochemistry was already fully determined by X-ray analysis.[3a] Arylation takes place in the conditions usually described in the literature:[8] oxazaphosphinane **1a** is arylated using catalytic amounts of tetrakis(triphenylphosphine) palladium (10 mol%), Ar–X (1 equiv), NEt_3 (3 equiv) under refluxing toluene to give as expected, only one diastereoisomer in good yields (69 to 75%) (Scheme 1, Table 1); indeed, these results are in accordance with the well established phosphorus retention of configuration during pallado-catalysed arylation.[9]



Scheme 1. Arylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes **1a**.

Table 1. Arylation of 2-*H*-2-oxo-1,4,2-oxazaphosphinane **1a**

Compound	Ar-X	Yield (%)[a]
7a	Ph-I	69
7b	*p*-Br-C_6H_4-I	73
7c	*p*-MeO-C_6H_4-Br	71
7d	2-Br-thiophene	70
7e	2-Br-pyridine	75

[a] Yield after purification by column chromatography.

Suitable crystals for X-ray analysis (Fig. 5) were obtained for the 2-pyridyl substituted compound **7e** after crystallization from chloroform. As noted above, retention of configuration at phosphorus atom is then confirmed (arylation occurs at the same side of the initial P–H bond). Moreover, we can point out the intramolecular H-bond between pyridyl nitrogen and proton of exocyclic amine. Using racemic oxazaphosphinane **1a**, both enantiomers appear on the crystal cell (Fig. 4). It is interesting to observe the π-stacking phenomenon between pyridyl and phenyl substituents of each enantiomer.

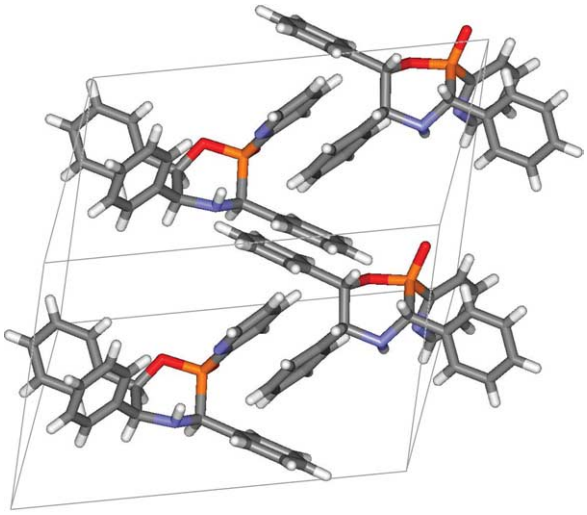


Figure 4. X-ray-cell of (+)-2-pyridyl-1,4,2-oxazaphosphinane **7e**.

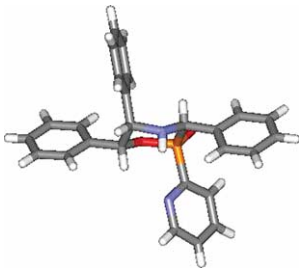
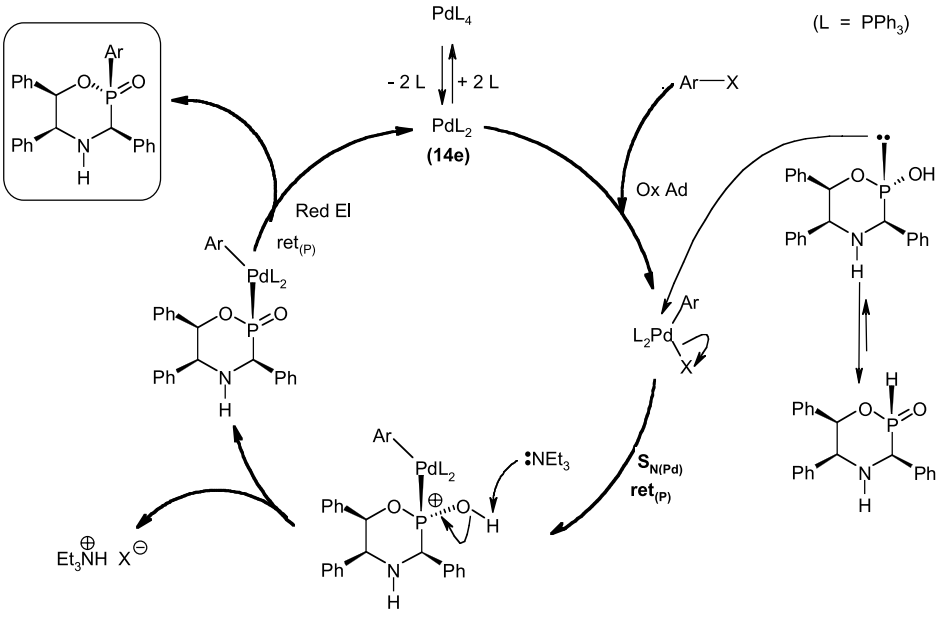


Figure 5. X-ray structure of 2-pyridyl-1,4,2-oxazaphosphinane **7f** derived from **1b**.

The mechanism of the catalysis also fully justifies the retention process (Scheme 2): The active catalyst PdL_2, a 14 electrons complex, gives a classical oxidative addition of the aryl halide and affords a 16 electrons intermediate. Further, the tetracoordinated oxazaphosphinane is stereoselectively in equilibrium, with the tricoordinated phosphinite form, which can give a nucleophilic substitution of



Scheme 2. Mechanism of the catalytic arylation.

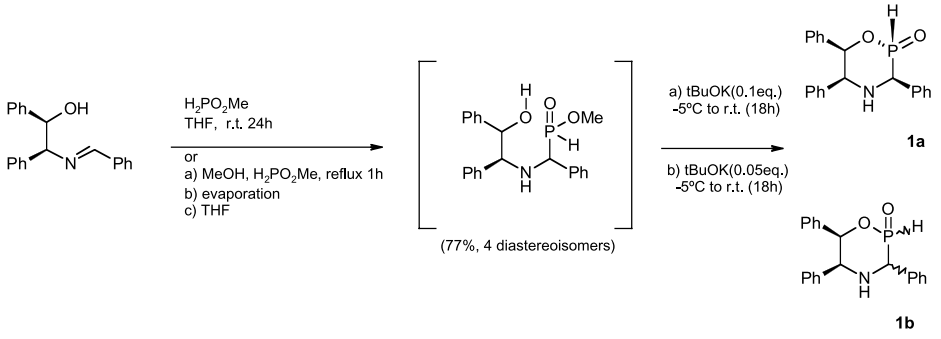
halogen (iodide or bromide) on palladium, and affords after deprotonation by the tertiary amine the metallated oxazaphosphinane with retention of configuration at phosphorus. The last step of catalytic cycle occurs also by a front reductive elimination with retention of configuration at phosphorus.

2.2. Determination of stereochemistry of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane 1b

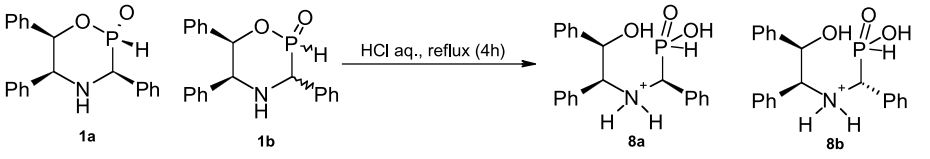
In our previous work dealing with synthesis of 2-*H*-2-oxo-1,4,2-oxazaphosphinane compounds,[3] two diastereoisomers **1a** and **1b** were obtained (Scheme 3). However, although we easily obtained suitable crystals of the diastereoisomer **1a** for X-ray analysis, we were unable to crystallize the second one **1b**.

Configurational relationship between **1a** and **1b** at C_3 position was easily demonstrated by ring opening of each compound with aqueous hydrochloric acid (Scheme 4): indeed, acidic treatment removes chirality at phosphorus center, then the C_3 chiral position only remains; treatment of a mixture of both diastereoisomers **1a** and **1b** leads to two opened structures **8a** and **8b**, they are consequently epimers at C_3 position. However, it was impossible to assign the stereochemistry of the phosphorus atom.

The full determination of relative stereochemistry of the second diastereoisomer **1b** not only at the C_3 position but also at the phosphorus center could be made by arylation of the second diastereoisomer with bromopyridine following the same procedure as described for arylations of **1a**. As expected, arylation of **1b** proceeds in a similar way (65% yield after column chromatography, one diastereoisomer **7f**)



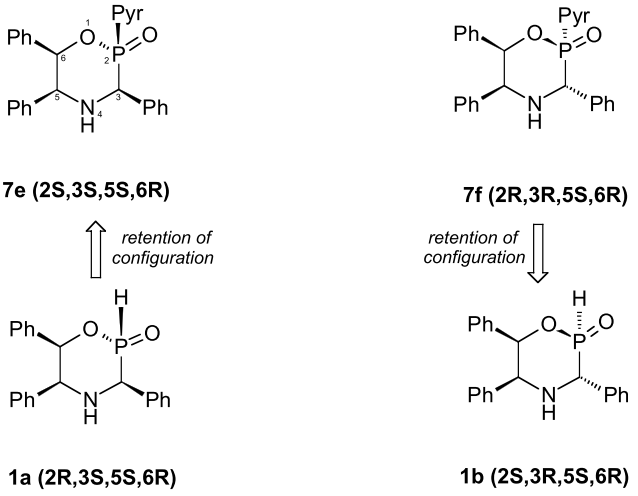
Scheme 3. 2-Hydrogeno-1,4,2-oxazaphosphinane synthesis via an intramolecular transesterification.



Scheme 4. Acidic ring opening to settle up the relative configurations at C_3 position.

and we were pleased to obtain suitable crystals by crystallization from chloroform for X-ray analysis, after chromatographic purification (Fig. 5).

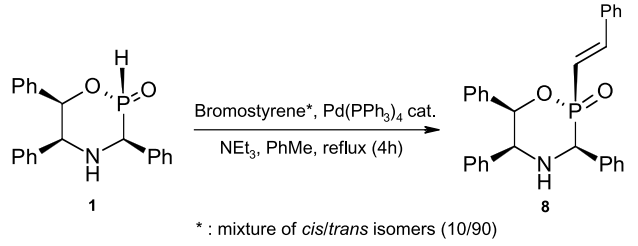
As compound **7f** has the pyridyl-group (P_2 position) and the phenyl-group (C_3 position) anti to the phenyl-groups at C_5 and C_6 positions, the relative stereochemistry of **1b** should be as follows (Scheme 5).



Scheme 5. Structure elucidation of diastereoisomer **1b**.

2.3. Vinylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane

Vinylation of oxazaphosphinane heterocycle was performed (Scheme 6) with β-bromo-styrene (a mixture of *cis*/*trans* isomers: 10/90). The first experiment using the same conditions as described above for arylation (110 °C, 4 h) afforded only one stereoisomer (*trans* compound as determined by ^{1}H NMR coupling constants) and no *cis* isomer coming from the starting β-bromostyrene is detected. At first glance, this result seems to be in contradiction with the well established stereospecificity of the reaction.



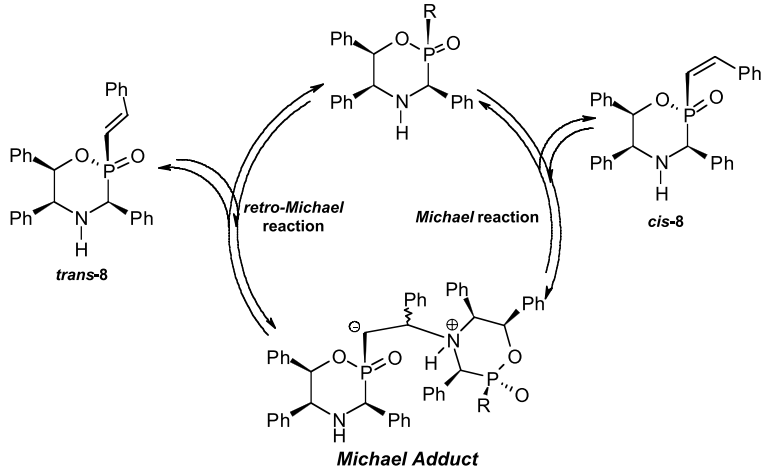
Scheme 6. Pallado-catalysed vinylation of 2-*H*-oxazaphosphinane **1a**.

A first explanation for the high *trans* stereoselectivity could consist with a preliminary in situ isomerisation of β-bromostyrene. Indeed, it is known that prolonged heating can isomerize the double bond to the thermodynamically more stable *trans*-derivative.[10] As a consequence, we tried to use softer conditions (55 °C, 1 h) but no presence of *cis*-derivative was detected leading us to make a NMR study of β-bromo-styrene isomerization under these reaction conditions. The reaction mixture (bromostyrene and triethylamine in deuterated benzene) checked by ^{1}H NMR analysis, after 1 h heating at 55 °C, shown that no isomerization occurred, even after addition of 10% $Pd(PPh_3)_4$ followed by 1 h heating.

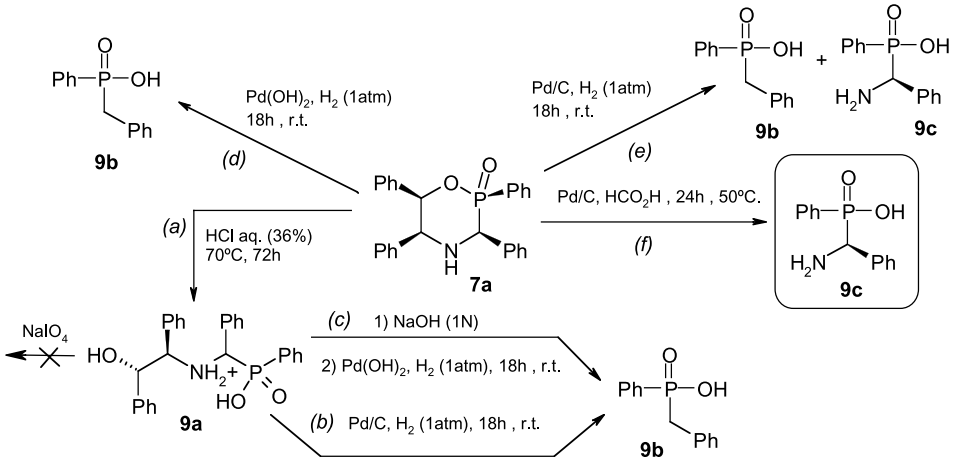
Another explanation could consist with in situ isomerization of vinyloxazaphosphinane due to its Michael olefin nature and presence of an intracyclic secondary amine function (Scheme 7). Indeed, it is well known that secondary amine catalyse isomerization of activated double bond from *cis* stereoisomer to *trans* one, as demonstrated for *cis*-chalcone[11] via Michael/*retro*-Michael reactions.

2.4. Deprotection of arylated 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane structure

Removal of the chiral inductor was carried out on the phenyl substituted compound **7a** (Scheme 8). Several ways could be considered: hydrogenolysis catalysed by palladium derivatives as well as oxidative cleavage by sodium periodate (as the inductor initially used is an aminoalcohol). The latter needs one more step for ring opening before oxidative cleavage, but the difficulty of hydrogenolysis consists on the regioselectivity of the cleavage due to the presence of two benzylic C–N bonds.



Scheme 7. Possible isomerization of *cis*-**8** catalysed by oxazaphosphinane secondary amine.



Scheme 8. 2-Phenyl-oxazaphosphinane deprotection to free phenyl-aminobenzylphosphinic acids.

Ring-opening of compound **9a** was easily obtained from cyclic starting material **7a** after acidic treatment (way a). However, sodium periodate gave no reaction even after several days.

Catalytic hydrogenolysis of **9a** over palladium on charcoal (way b) or palladium hydroxide (way c) (after neutralisation by aqueous NaOH 1 N solution) under 1 atm of hydrogen was tried but gave unfortunately the wrongly deprotected benzyl-phenylphosphinic acid **9b**, leading us to try hydrogenolysis directly to the arylated heterocycle **7a**. As above, palladium hydroxide leads to the wrong deprotected derivative **9b** (way d). Surprisingly, palladium on charcoal gave the expected α-aminobenzyl-phenylphosphinic acid **9c**, with small amount of **9b** (way e). These results incited us to choose mild hydrogen donor as formic acid under Pd/C catalysis: in such conditions (way f), very clean reaction occurred affording only the correctly deprotected compound **9c** with high isolated yield (75%). Petnehazy et al. recently described[12] the deprotection of *N*-methylbenzyl-α-amino benzylphosphinic acid to compound **9c** using Pd/C hydrogenolysis under 10 atm of hydrogen. However, according to the chemical shifts (^{31}P and ^{1}H NMR) and melting point given, it is likely that they actually isolated compound **9b**.

3. Conclusion

In conclusion, we synthesized several aryl or heteroaryl oxazaphosphinanes via a palladium(0) catalysed arylation of 2-hydrogeno-1,4,2-oxazaphosphinane with aromatic or heteroaromatic bromides or iodides affording heterocyclic phosphorus analogues of arylated morpholinols. Furthermore, vinylation of these structures was also tried to afford activated olefin containing chiral functionalized phosphinate moiety, usable for several diastereoselective reactions (Michael addition, Diels–Alder reactions…). Cleavage of the chiral inductor using catalytic hydrogenolysis was finally described opening new perspectives in the synthesis of α-aminophosphinic derivatives.

4. Experimental

All reactions involving air or moisture sensitive reagents or intermediates were carried out under dry nitrogen in flame-dried glassware. Reagents and solvents were distilled before use and stored under nitrogen over sodium wires (THF) or molecular sieves (dichloromethane). All reactions were monitored by ^{31}P NMR. Merck silica gel (35–70 μm) was used for column chromatography. NMR spectra were recorded on BRUKER AC 200, 250 or 400 (^{1}H frequency: 200.13, 250.13 or 400.13 MHz; ^{13}C frequency: 50.32, 62.89 or 100.62 MHz, ^{31}P frequency: 81.02, 101.25, 162.04 MHz, respectively). Chemical shifts are given in δ units with respect to TMS (^{1}H, ^{13}C NMR) or H_3PO_4 85% (^{31}P), coupling constants are expressed in Hz. Infrared spectra were recorded on PERKIN-ELMER 377 or FT-NICOLET 210 spectrometer. Mass spectra were measured on JEOL JMS DX-300 spectrometer (positive FAB ionisation and High Resolution using *p*-nitrobenzyl alcohol NBA).

4.1. General procedure for arylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane (7a–7f, 8)

In a 10 ml flask containing 675 mg of **1a** (1.94 mmol) and 224 mg of palladium-tetrakis(triphenylphosphine) (0.194 mmol, 0.1 equiv) under N_2 are added under stirring 3.7 ml of dry toluene followed by 810 μL of triethylamine (5.82 mmol) and aryl-halide or vinyl-halide (1.94 mmol) at room temperature. The reaction mixture is heated at 110 °C and precipitation of triethylammonium halide occurs. After 4 h stirring at 110 °C, compound **1a** was completely consumed and heating was stopped. After cooling, the reaction mixture is dissolved in chloroform and saturated aqueous NaCl solution is added. After extraction with chloroform, the organic layers are dried over Na_2SO_4. The crude solution is evaporated affording a solid purified by column chromatography (dichloromethane/ethyl acetate gradient: 100/0 to 50/50).

4.1.1. (2*R,3*R**,5*R**,6*S**)-(+/−)-2-Oxo-2,3,5,6-tetraphenyl-1,4,2-oxazaphosphinane 7a.** White solid (570 mg, 1.34 mmol, 1 diastereoisomer), mp = 223.9 °C; yield 69%;

^{31}P NMR (81.02 MHz, $CDCl_3$): 42.77; ^{1}H NMR (250.13 MHz, $CDCl_3$): 2.20 (d, 1H, $^{3}J_{PH}$=28.9 Hz, NH), 4.93 (dd, 1H, $^{3}J_{HH}$=4.6, 4.6 Hz, NC*H*Ph), 5.13 (d, 1H, $^{2}J_{PH}$=13.4 Hz, PC*H*Ph), 6.20 (dd, 1H, $^{3}J_{PH}$=7.1 Hz, $^{3}J_{HH}$=5.8 Hz, OC*H*Ph), 7.18–7.80 (m, 20H, C*Har*): ^{13}C NMR (MHz, DMSO-d_6): 59.60 (d, $^{1}J_{PC}$=106.5 Hz, HN*C*HP), 63.36 (s, N*C*HPh), 76.47 (d, $^{2}J_{PC}$=4.8 Hz, O*C*HPh), 127.09–129.56 (m, *C*Har), 136.17 (d, $^{2}J_{PC}$=5.8 Hz, *C*ar), 137.95 (d, $^{3}J_{PC}$=8.2 Hz, *C*ar), 141.04 (s, *C*ar), 139.19 (d, $^{2}J_{PC}$=9.1 Hz, PCar*C*Har): IR (KBr): 3440, 3280, 3080, 3020, 2840, 1590, 1480, 1450, 1230, 1200, 1180, 1125, 1060, 1030, 990, 690; HRMS (FAB$^+$): calcd for $C_{27}H_{24}NO_2P$ 425.1623. Found 425.1605; 426 $[M+H]^+$ (32%), 284 (95%), 180 (100%), 106 (21%), 91 (38%).

4.1.2. (2*R,3*R**,5*R**,6*S**)-(+/−)-2-Oxo-3,5,6-triphenyl-2-*p*-bromophenyl-1,4,2-oxazaphosphinane 7b.** White solid (714 mg, 1.42 mmol, 1 diastereoisomer), mp=228.8 °C; 73% yield; ^{31}P NMR (81.02 MHz, $CDCl_3$): 42.05: ^{1}H NMR (250.13 MHz, $CDCl_3$): 2.23 (d, 1H, $^{3}J_{PH}$=30.3 Hz, NH), 4.91 (dd, 1H, $^{3}J_{HH}$=4.3 Hz, $^{3}J_{HH}$=4.3 Hz, N C*H*Ph), 5.13 (d, 1H, $^{2}J_{PH}$=13.0 Hz, PC*H*Ph), 6.18 (dd, 1H, $^{3}J_{PH}$=7.3 Hz, $^{3}J_{HH}$=5.7 Hz, OC*H*Ph), 7.17–7.57 (m, 19H, C*Har*): ^{13}C NMR (52.32 MHz, DMSO-d_6): 59.18 (d, $^{1}J_{PC}$=100.9 Hz, HN*C*HP), 62.18 (s, N*C*HPh), 75.68 (d, $^{2}J_{PC}$=4.5 Hz, O*C*HPh), 126.19–128.58 (m, *C*Har), 131.04 (d, $^{2}J_{PC}$=13.0 Hz, *C*ar), 134.37 (d, $^{2}J_{PC}$=9.7 Hz, *C*ar), 135.21 (d, $^{2}J_{PC}$=5.6 Hz, *C*arCH[(P),(NH)]), 137.07 (d, $^{3}J_{PC}$=8.9 Hz, *C*arCH[(O),(CH)]), 140.0 (s, *C*arCHN), 137.07 (d, $^{2}J_{PC}$=8.9 Hz, PCar*C*Har): IR (KBr): 3360, 3290, 3080, 3020, 2860, 1600, 1490, 1450, 1240, 1190, 1120, 1070, 1030, 990, 960, 690; HRMS (FAB$^+$): calcd for $C_{27}H_{23}BrNO_2P$: 503.0728. Found: 503.0673; 504 $[M+H]^+$ (24%), 284 (100%), 180 (67%), 106 (20%), 91 (27%).

4.1.3. (2*R,3*R**,5*R**,6*S**)-(+/−)-2-Oxo-3,5,6-triphenyl-2-p-methoxyphenyl-1,4,2-oxazaphosphinane 7c.** White solid (627 mg, 1.38 mmol, 1 diastereoisomer), mp=233.1 °C; 71% yield: ^{31}P NMR (81.02 MHz, $CDCl_3$): 42.95: ^{1}H NMR (250.13 MHz, $CDCl_3$): 2.15 (d, 1H, $^{3}J_{PH}$=28.4 Hz, N*H*), 3.80 (s, 3H, CH_3), 4.86 (dd, 1H, $^{3}J_{HH}$=4.5 Hz, $^{3}J_{HH}$=5.1 Hz, NC*H*Ph), 5.07 (d, 1H, $^{2}J_{PH}$=12.5 Hz, PC*H*Ph), 6.16 (dd, 1H, $^{3}J_{PH}$=7.2 Hz, $^{3}J_{HH}$=5.9 Hz, OC*H*Ph), 7.14–7.59 (m, 19H, *CH*ar); ^{13}C NMR (62.90 MHz, DMSO-d_6): 56.17 (s, *C*H$_3$), 60.30 (d, $^{1}J_{PC}$=99.8 Hz, HN*C*HP), 63.27 (s, N*C*HPh), 76.09 (d, $^{2}J_{PC}$=4.8 Hz, O*C*HPh), 114.41 (d, $^{2}J_{PC}$=13.9 Hz, PCar*C*H), 119.27 (d, $^{1}J_{PC}$=140.1 Hz, P*C*ar), 127.09–129.56 (m, *C*Har), 135.42 (d, $^{3}J_{PC}$=10.6 Hz, MeOCar*C*Har), 136.71 (d, $^{2}J_{PC}$=5.3 Hz, *C*arCH[(P),(NH)]), 138.32 (d, $^{3}J_{PC}$=8.2 Hz, *C*arCH[(O),(CH)]), 141.21 (s, *C*arCHN), 163.34 (d, $^{4}J_{PC}$=2.9 Hz, MeO*C*ar): IR (KBr): 3270, 3080, 3020, 2960, 2820, 1600, 1490, 1450, 1260,1230, 1180, 1130, 1060, 1030, 990, 950, 700; HRMS (FAB$^+$): calcd for $C_{28}H_{26}NO_3P$: 455.1729. Found: 455.1729; 456 $[M+H]^+$ (29%), 284 (100%), 180 (80%), 106 (10%), 91 (15%).

4.1.4. (2*R,3*R**,5*R**,6*S**)-(+/−)-2-Oxo-3,5,6-triphenyl-2-(2-thienyl)-1,4,2-oxazaphosphinane 7d.** White solid (653 mg, 1.51 mmol, 1 diastereoisomer), mp=224.8 °C; 78% yield: ^{31}P NMR (81.02 MHz, $CDCl_3$): 38.39; ^{1}H NMR (250.13 MHz, $CDCl_3$): 2.25 (d, 1H, $^{3}J_{PH}$=28.9 Hz, N*H*), 4.84 (dd, 1H, $^{3}J_{HH}$=4.4 Hz, $^{3}J_{HH}$=4.4 Hz, NC*H*Ph), 5.14 (d, 1H, $^{2}J_{PH}$=11.5 Hz, PC*H*Ph), 6.18 (dd, 1H, $^{3}J_{PH}$=8.4 Hz, $^{3}J_{HH}$=5.8 Hz, OC*H*Ph), 7.04–7.41 (m, 17H, C*H*ar), 7.68 (dd, 1H, $^{3}J_{HH}$=3.8 Hz, $^{4}J_{HH}$=3.8 Hz, SC*H*); ^{13}C NMR (62.90 MHz, DMSO-d_6): 59.61 (d, $^{1}J_{PC}$=107.0 Hz, HN*C*HP), 63.37 (s, N*C*HPh), 76.48 (d, $^{2}J_{PC}$=4.8 Hz, O*C*HPh), 127.0–129.73 (m, *C*Har), 136.51 (d, $^{4}J_{PC}$=4.3 Hz, S*C*Har), 136.17 (d, $^{2}J_{PC}$=6.2 Hz, *C*arCH[(P),(NH)]), 137.95 (d, $^{3}J_{PC}$=8.6 Hz, *C*arCH[(O),(CH)]), 141.04 (s, *C*arCHN), 139.20 (d, $^{4}J_{PC}$=11.0 Hz, [(P),(S)]Car*C*H): IR (KBr): 3420, 3270, 3080, 3030, 2990, 2840, 1600, 1490, 1450, 1230, 1200, 1130, 1060, 1030, 990, 955, 700, 695; HRMS (FAB$^+$): calcd for $C_{25}H_{22}NO_2PS$: 431.1187. Found: 431.1196; 432 $[M+H]^+$ (43%), 284 (100%), 180 (73%), 106 (11%), 91 (19%).

4.1.5. (2*S,3*S**,5*R**,6*S**)-(+/−)-2-Oxo-3,5,6-triphenyl-2-(2-pyridyl)-1,4,2-oxazaphosphinane 7e.** White solid (620 mg, 1.46 mmol, 1 diastereoisomer), mp=221.2 °C; 75% yield: ^{31}P NMR (81.02 MHz, $CDCl_3$): 34.52; ^{1}H NMR (250.13 MHz, $CDCl_3$): 3.47 (ddd, 1H, $^{3}J_{PH}$=20.7 Hz, $^{3}J_{HH}$=9.2, 11.9 Hz, N*H*), 4.78 (dd, 1H, $^{3}J_{HH}$=6.5, 7.7 Hz, NC*H*Ph), 5.10 (dd, 1H, $^{2}J_{PH}$=16.1 Hz, $^{3}J_{HH}$=11.7 Hz, PC*H*Ph), 6.21 (dd, 1H, $^{3}J_{PH}$=7.9 Hz, $^{3}J_{HH}$=5.7 Hz, OC*H*Ph), 7.08–7.48 (m, 16H, C*H*ar), 7.68 (m, 1H, [N,P]CarCHC*H*ar), 7.93 (dd, 1H, $^{2}J_{PH}$=7.3 Hz, $^{3}J_{HH}$=7.3 Hz, [P,N]CarC*H*ar), 7.93 (d, 1H, $^{3}J_{HH}$=4.4 Hz, NC*H*ar); ^{13}C NMR (50.32 MHz, $CDCl_3$): 58.60 (d, $^{1}J_{PC}$=83.0 Hz, HN*C*HP), 65.05 (d, $^{4}J_{PC}$=1.5 Hz, N*C*HPh), 76.92 (d, $^{2}J_{PC}$=6.3 Hz, O*C*HPh), 127.09–129.56 (m, *C*Har), 134.30 (d, $^{3}J_{PC}$=1.1 Hz, [P,N]CarCHar*C*Har), 136.52 (d, $^{2}J_{PC}$=6.3 Hz, *C*arCH[(P),(NH)]), 135.96 (d, $^{3}J_{PC}$=10.4 Hz, *C*arCH[(O),(CH)]), 138.89 (s, *C*arCHN), 149.59 (d, $^{3}J_{PC}$=19.3 Hz, N*C*Har), 151.86 (d, $^{1}J_{PC}$=163.0 Hz, P*C*ar); IR (KBr): 3420, 3270, 3080, 3020, 2920, 1590, 1490, 1450, 1250, 1230, 1185, 1155, 1090, 1060, 1010, 990, 950, 710, 690; HRMS (FAB$^+$): calcd for $C_{26}H_{23}N_2O_2P$: 426.1575. Found: 426.1558; 427 $[M+H]^+$ (45%), 284 (100%), 180 (54%), 106 (8%), 91 (16%).

4.1.6. (2*R,3*R**,5*S**,6*R**)-(+/−)-2-Oxo-3,5,6-triphenyl-2-(2-pyridyl)-1,4,2-oxazaphosphinane 7f.** White solid (618 mg, 1.45 mmol, 1 diastereoisomer), mp=221.2 °C; 75% yield: ^{31}P NMR (81.02 MHz, $CDCl_3$): 24.55; ^{1}H NMR (250.13 MHz, $CDCl_3$): 3.36 (bs, 1H, N*H*), 4.17 (d, 1H, $^{3}J_{HH}$=3.2 Hz, N C*H*Ph), 4.12 (d, 1H, $^{2}J_{PH}$=19.4 Hz, PC*H*Ph), 7.15 (m, 1H, OC*H*Ph), 7.13–7.65 (m, 18H, C*H*ar), 8.75 (m, 1H, NC*H*ar): ^{13}C NMR (62.90 MHz, $CDCl_3$): 56.31 (d, $^{1}J_{PC}$=99.6 Hz, HN*C*HP), 61.93 (d, $^{4}J_{PC}$=3.1 Hz, NC*H*Ph), 86.46 (d, $^{2}J_{PC}$=10.0 Hz, OC*H*Ph), 125.44–130.59 (all C*H*ar), 134.87 (d, $^{3}J_{PC}$=1.9 Hz, Car), 138.34 (d, $^{2}J_{PC}$=6.2 Hz, *C*ar), 136.33 (d, $^{3}J_{PC}$=10.8 Hz, *C*ar), 136.50 (s, *C*ar), 149.61 (d, $^{3}J_{PC}$=21.5 Hz, N*C*Har), 154.52 (d, $^{1}J_{PC}$=166.9 Hz, P*C*ar): IR (KBr): 3430, 3300, 3080, 3020, 2920, 2860, 1595, 1490, 1445, 1270,1230, 1170, 1110, 1070, 1040, 1025, 970, 690; HRMS (FAB$^+$): calcd for $C_{26}H_{23}N_2O_2P$ 426.1575. Found: 426.1586; 427 $[M+H]^+$ (44%), 284 (80%), 180 (49%), 106 (24%), 91 (29%).

4.1.7. Vinylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane 1a; (2*R,3*R**,5*R**,6*S**)-(+/−)-2-oxo-3,5,6-triphenyl-2-styryl-1,4,2-oxazaphosphinane 8.** White solid

(604 mg, 1.34 mmol, 1 diastereoisomer), mp = 196.4 °C; 69% yield; ^{31}P NMR (81.02 MHz, $CDCl_3$): 39.12; ^{1}H NMR (250.13 MHz, $CDCl_3$): 2.26 (bm, 1H, $^3J_{PH}$ = 29.2 Hz, N*H*), 4.87 (dd, 1H, $^3J_{HH}$ = 4.1, 4.1 Hz, NC*H*Ph), 5.01 (d, 1H, $^2J_{PH}$ = 13.9 Hz, PC*H*Ph), 5.98 (dd, 1H, $^3J_{PH}$ = 8.2 Hz, $^3J_{HH}$ = 4.1 Hz, OC*H*Ph), 6.20 (dd, 1H, $^2J_{PH}$ = 21.5 Hz, $^3J_{HH}$ = 17.4 Hz, vinyl), 7.14–7.62 (m, 20H, C*H*ar); ^{13}C NMR (50.32 MHz, DMSO-d_6): 62.53 (d, $^1J_{PC}$ = 99.3 Hz, HN*C*HP), 63.91 (d, $^3J_{PC}$ = 1.6 Hz, N*C*HPh), 79.57 (d, $^2J_{PC}$ = 7.5 Hz, O*C*HPh), 114.19 (d, $^1J_{PC}$ = 156.2 Hz, P*C*HCH), 127.54–130.56 (m, *C*Har), 135.99 (d, $^2J_{PC}$ = 5.9 Hz, *C*arCH[(P),(NH)]), 136.75 (d, $^3J_{PC}$ = 7.5 Hz, *C*arCH[(O),(CH)]), 139.24 (s, *C*arCHN), 135.46 (d, $^2J_{PC}$ = 22.4 Hz, PCH*C*H), 150.56 (d, $^1J_{PC}$ = 156.2 Hz, CHCH*C*ar); IR (KBr): 3420, 3290, 3080, 3020, 2840, 1590, 1485, 1440, 1230, 1210, 1190, 1180, 1090, 1060, 1025, 990, 955, 700; HRMS (FAB$^+$): calcd for $C_{29}H_{26}NO_2P$ 451.1779. Found: 451.1768; 452 $[M+H]^+$ (35%), 284 (100%), 180 (58%), 106 (8%), 91 (18%).

4.2. General procedure for deprotection of arylated 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane compounds

4.2.1. α-[(2-Hydroxy-1,2-diphenyl-ethylamino)-benzyl]-phenyl-phosphinic acid 9a. In a 250 ml flask containing 800 mg of **7a** (1.75 mmol) is added 50 ml of concentrated aqueous HCl solution (35%). Under stirring, the reaction mixture is heating 3 days at 80 °C. Then, after cooling, the reaction mixture is dissolved in chloroform and saturated with aqueous NaCl solution. After extraction with chloroform, the organic layers are dried over Na_2SO_4. The crude solution is evaporated affording a yellow-brown solid purified by column chromatography (dichloromethane/ Ethyl acetate gradient: 100/0 to 70/30).

White solid (780 mg, 1.76 mmol, 1 diastereoisomer), mp = 209.6 °C; 92% yield; ^{31}P NMR (81.02 MHz, DMSO-d_6): 28.93: ^{1}H NMR (250.13 MHz, DMSO-d_6): 4.45 (d, 1H, $^2J_{PH}$ = 12.0 Hz, PC*H*Ph), 4.49 (d, 1H, $^3J_{HH}$ = 2.4 Hz, NC*H*Ph), 5.53 (d, 1H, $^3J_{HH}$ = 2.4 Hz, OC*H*Ph), 6.88–7.53 (m, 20H, C*H*ar); ^{13}C NMR (100.62 MHz, DMSO-d_6): 60.38 (d, $^1J_{PC}$ = 95.8 Hz, HN*C*HP), 67.14 (s, N*C*HPh), 71.15 (s, O*C*HPh), 125.97–132.18 (all *C*Har), 130.97 (d, $^1J_{PC}$ = 133.9 Hz, *C*ar), 135.92 (s, *C*ar), 141.03 (s, *C*ar); IR (KBr): 3260, 3130, 3040, 2920, 1585, 1490, 1440, 1425, 1450, 1220, 1190, 1070, 950, 700; HRMS (FAB$^+$): calcd for $C_{27}H_{26}NO_3P$ 443.1729. Found: 443.1716; 444 $[M+H]^+$ (21%), 887 $[2M+H]^+$ (10%), 302 (100%), 284 (51%), 180 (11%), 106 (100%).

4.2.2. Benzyl-phenyl-phosphinic acid 9b. A 10 ml flask, containing 300 mg (0.71 mmol) of **7a**, 300 mg of palladium catalyst [$Pd(OH)_2$] and 5ml of methanol is placed under hydrogen atmosphere (1 atm). After 18 h stirring at ambient temperature, reaction mixture is filtrated over celite, and the filtrate evaporated. 2 ml of aqueous solution of NaOH (1 N) are added. After 3 h stirring, the milky suspension is filtered and rinsed with 1 ml water. Filtrate is precipitated by acidification to pH = 5 with aqueous HCl solution (1 N). Final filtration afforded pure **9b**.

White solid (127 mg, 0.55 mmol), mp = 187.2 °C; 92% yield; ^{31}P NMR (101.25 MHz, CD_3OD): 38.87; ^{1}H NMR (250.13 MHz, CD_3OD): 3.32 (d, 2H, $^2J_{PH}$ = 17.9 Hz, PC*H*Ph), 7.07–7.68 (m, 10H, *CH*ar); ^{13}C NMR (50.32 MHz, CD3OD): 37.70 (d, $^1J_{PC}$ = 94.2 Hz, HN*C*HP), 126.04–132.70 (all *C*Har), 131.40 (d, $^1J_{PC}$ = 130.6 Hz, P*C*ar); IR (KBr): 3040, 3020, 2990, 2860, 1650, 1455,1440, 1240, 1200, 1170, 1140, 960, 700; HRMS (FAB$^+$): calcd for $C_{13}H_{13}O_2P$ 233.0731. Found: 233.0735; 233 $[M+H]^+$ (100%), 91 (45%): 77 (30%).

4.2.3. α-Aminobenzyl-phenylphosphinic acid 9c. In a 10 ml flask containing 300 mg (0.71 mmol) of **7a** and 300 mg of palladium catalyst (Pd/C 10% on activated charcoal, 0.28 mmol) is added 10.6 ml of methanolic solution of formic acid (10% vol/vol). After 3 h stirring at 55 °C, the reaction mixture is filtrated over celite, and the filtrate evaporated. 2 ml of aqueous solute of NaOH (1 N) are added. The suspension is then filtered and the filtrate is evaporated. The white solid is recrystallized in methanol to afford **9c** as white crystals.

White solid, (132 mg, 0.53 mmol, 1 diastereoisomer), mp = 205.8 °C; 75% yield; ^{31}P NMR (101.25 MHz, CD_3OD): 32.16; ^{1}H NMR (250.13 MHz, CD_3OD): 4.27 (d, 1H, $^2J_{PH}$ = 12.0 Hz, PC*H*Ph), 7.23–7.47 (m, 20H, C*H*ar); ^{13}C NMR (62.90 MHz, CD_3OD): 57.29 (d, $^1J_{PC}$ = 96.5 Hz, HN*C*HP), 127.24–132.28 (all *C*Har), 134.00 (d, $^1J_{PC}$ = 122.4 Hz, P*C*ar), 139.01 (d, $^2J_{PC}$ = 1.9 Hz, *C*arCHP); IR (KBr): 3240, 3000, 1600, 1490, 1430, 1200, 1170,1130, 1045, 1000, 690, 570, 545,490; HRMS (FAB$^+$): calcd for $C_{13}H_{14}NO_2P$ 248.0840. Found 248.0848; 248 $[M+H]^+$ (12%), 106 (33%), 77 (24%). (N° CAS: 25891-89-8).

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