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Chiral phosphinyl analogues of 2-*C*-arylmorpholinols: 2-aryl-3,5-diphenyl-[1,4,2]-oxazaphosphinanes

Jean-Noël Volle,* David Virieux, Matthieu Starck, Jérôme Monbrun, Ludovic Clarion and Jean-Luc Pirat*

Laboratoire de Chimie Organique, UMR CNRS 5076, Ecole Nationale Supérieure de Chimie de Montpellier, 8, Rue de l'Ecole Normale, 34296 Montpellier Cedex 5, France

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Abstract—(2*R*,3*R*,5*R*)-2-Aryl-3,5-diphenyl-[1,4,2]-oxazaphosphinanes **6**, analogues of *C*-arylmorpholinol **3**, were prepared with diastereomeric excess higher than 94%, via a three step sequence: (i) diastereoselective addition–cyclization reaction from methyl hypophosphite and a chiral imine **10**, (ii) pallado-catalyzed arylation, and then (iii) a selective inversion of configuration at the phosphorus center.

1. Introduction

Bupropion **1** is an active ingredient of Wellbutrin®, which is marketed in the United States for the treatment of depression. It mainly metabolizes into hydroxybupropion **2**,[1] which is twice as selective toward the noradrenergic system than bupropion itself.[2] Thereafter, a structure–activity relationship study on the 2-arylmorpholinol core allowed the discovery of compound **3**,[3] which possesses a 15-fold higher in vitro specific affinity than **2** toward the enzymes responsible for the capture of noradrenaline.[4] The strong activity of 2-arylmorpholinols on the noradrenergic systems could thus provide a new therapeutic means for the treatment of depression and attention deficit hyperactivity disorder (ADHD) (Fig. 1).

We envisioned oxazaphosphinanes **6** as structural analogues of *C*-arylmorpholinol **3**. In continuation of our previous work on oxazaphosphinanes **4** and **5**,[5] we herein report the synthesis of chiral oxazaphosphinanes **6** in both enantiomeric forms. The preparation of compound **6** required the creation of two vicinal stereogenic centers. They were introduced by a three step procedure, a diastereoselective addition–cyclization reaction, followed by arylation and then by a selective epimerization at the phosphorus center under thermodynamic conditions (Fig. 2).

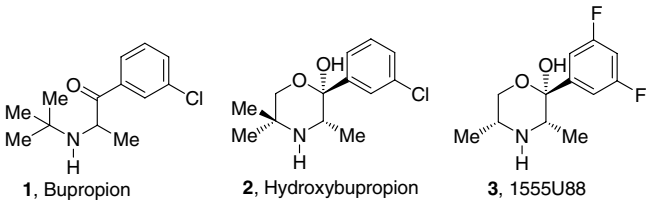

Figure 1. Antidepressants: bupropion **1** and 2-*C*-arylmorpholinols **2**–**3**.

A ^{1}H NMR study allowed us to determine both the relative and absolute configurations of the two newly created stereogenic centers in accordance with X-ray diffraction experiments.

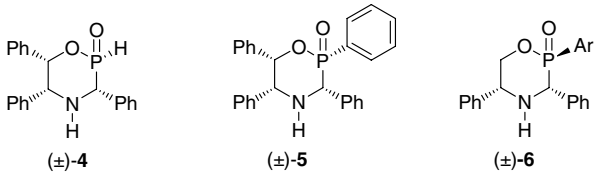

Figure 2. Structural analogy between *P*-aryl-1,4,2-oxazaphosphinanes **6** and 2-*C*-arylmorpholinols **2**–**3**.

2. Results and discussion

According to the retrosynthetic analysis shown in Scheme 1, the thermodynamic oxazaphosphinane **6** could be

* Corresponding authors. Fax: +33 4 67144319; e-mail addresses: jean-noel.volle@enscm.fr; pirat@enscm.fr

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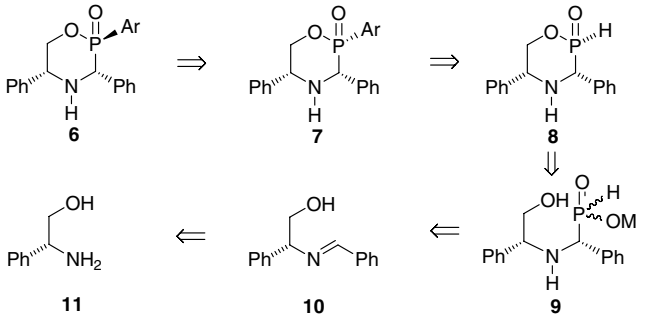
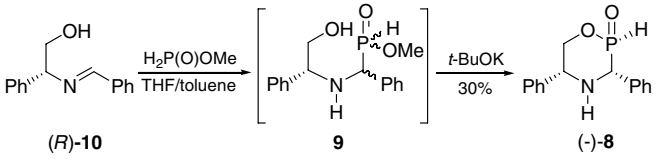


Scheme 1. Retrosynthetic analysis for compound **6**.

obtained from compound **7** by inversion of configuration at the phosphorus center leading to the more stable *trans* isomer. This epimerization could be carried out under acidic conditions, as mentioned for a cyclic phosphonate.[6] As for obtention of compound **5**, **7** could be easily accessible from oxazaphosphinane **8**, by palladium catalyzed coupling of the corresponding aryl halide. The main point of interest for this reaction is the complete retention of configuration observed at the phosphorus center.[5c] The other retrosynthetic steps are based on previously described diastereoselective nucleophilic addition followed by cyclization of methyl hypophosphite to a chiral imino alcohol.

(*R*)-Imino alcohol **10** was prepared via condensation of (*R*)-glycinol **11** with benzaldehyde in dichloromethane in the presence of sodium sulfate as the drying agent. Methyl hypophosphite was obtained according to a methodology already developed in the laboratory by mixing hypophosphorous acid and trimethyl-orthoformate in toluene/THF (1:1).[7] Contrary to the synthesis of compound **4**, acyclic intermediates **9** could not be identified by ^{31}P NMR after dilution of the reaction mixture with THF and addition of imine (*R*)-**10**. However at this stage, the main signal at 32.6 ppm (formation rate 20%) was assigned to the cyclic compound (−)-**8**. The addition of a 40% molar solution of potassium *tert*-butoxide in THF allowed us to obtain 40–50% yield of compound (−)-**8**.

All these observations showed that the cyclization partially occurred before the basic treatment. The differences in the reactivity noticed between acyclic intermediates **9** and those observed for the preparation of **4**, can be attributed to the stronger nucleophilicity of the primary hydroxyl group in intermediate **9** in comparison with the secondary alcohol involved in the formation of **4**.[5a] After work-up and column chromatography on silica gel, oxazaphosphinane (−)-**8** was isolated in 30% yield. Enantiomer (+)-**8** was prepared from (*S*)-**10** in identical yield using the same procedure (Scheme 2).



Scheme 2. Preparation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane **8**.

The three-dimensional structure and the configuration of the two newly created stereogenic centers were determined by an X-ray experiment on a monocrystal of (+)-**8** obtained by crystallization from dichloromethane.[8a] As expected, the P–H bond and the 3-phenyl group were in a *cis* position relative to the 5-phenyl substituent.[5d] The six-membered ring showed a preferred chair conformation, where the two phenyl groups occupy an equatorial position (Fig. 3). Interestingly, the ^{1}H NMR spectra were also useful for the determination of the absolute configuration of both phosphorus and carbon atoms. The spectra exhibited two independent AX and ABCX spin systems. In fact, in the AX systems involving a (O)PCH linkage, $^{2}J_{PH}$ coupling constants are sensitive to the dihedral angles O–P–C–H. These generally have a minimal value (−14 to −18 Hz) for a *gauche* conformation and a maximum value (−5 to 0 Hz) for a 180° dihedral angle.[9] In the same way, the dihedral angular dependence for $^{3}J_{PH}$ in the six-membered heterocyclic ring system –POCH$_2$– indirectly allowed the determination of the configuration of the phosphorus atom by attribution of the *cis* $^{3}J_{HaHc}$ and *trans* $^{3}J_{HbHc}$ coupling constants.

Thereafter, the complete determination of the coupling constants $^{2}J_{PH}$ for H$_d$ proton and $^{3}J_{PH}$, $^{3}J_{HH}$ for H$_a$, H$_b$ and H$_c$ for compound **8** was undertaken in deuterated acetone (Fig. 3).[10] Thus, coupling constant values were: $^{2}J_{PHd} = -15.4$ Hz for the AX system and $^{3}J_{PHa} = 21.5$ Hz and $^{3}J_{PHb} = 3.6$ Hz. The *Karplus* relationships between H$_c$ and H$_a$ or H$_c$ and H$_b$ were also determined to be $^{3}J_{HaHc} = 2.1$ Hz and $^{3}J_{HbHc} = 10.5$ Hz. These were in good agreement with those described for the *gauche* and the *anti* conformation of morpholines.[11] These different coupling constants allowed us to conclude that compound **8**, in solution, has the same conformation as observed for the solid state (Fig. 3).

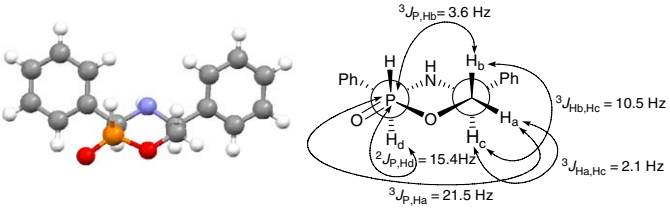
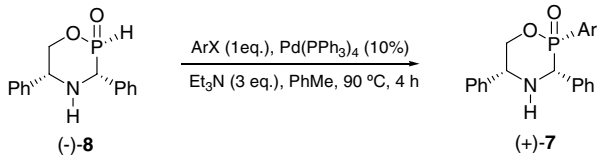


Figure 3. X-ray structure and ^{1}H NMR analysis of (+)-**8**.

Pallado-catalyzed arylation of (−)-oxazaphosphinane **8** took place using conditions previously developed and depicted (Scheme 3). 2-Aryl-[1,4,2]-oxazaphosphinanes (+)-**7** were prepared in 64–75% yields as a single diastereomer. Similarly, the same reactions were carried out with enantiomer (+)-**8**, whose results are given in Table 1.

The retention of configuration previously observed during the arylation process was also confirmed for compound (−)-**7b**, after an X-ray experiment on a monocrystal obtained from ethyl acetate/chloroform.[8b] Structure **7b** adopted a chair conformation where the *cis* *P*-aryl group was in an axial position (Fig. 4).



Scheme 3. Arylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinane (−)-**8**.

Table 1. Arylation of 2-*H*-2-oxo-1,4,2-oxazaphosphinane **8**

Compound	Ar–X	Yield (%)[a]	
		(+)-Enantiomer	(−)-Enantiomer
7a	Ph–I	74	70
7b	*p*-MeO–C_6H_4–I	73	75
7c	*p*-Br–C_6H_4–I	68	69
7d	*m*-Cl–C_6H_4–I	73	72
7e	3,5-F_2–C_6H_3–Br	69	64

[a] Yield after purification by column chromatography.

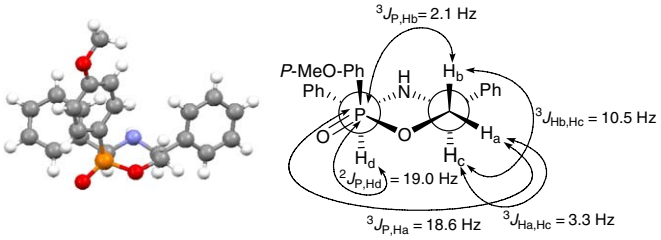


Figure 4. X-ray structure and ^{1}H NMR analysis of (+)-**7b**.

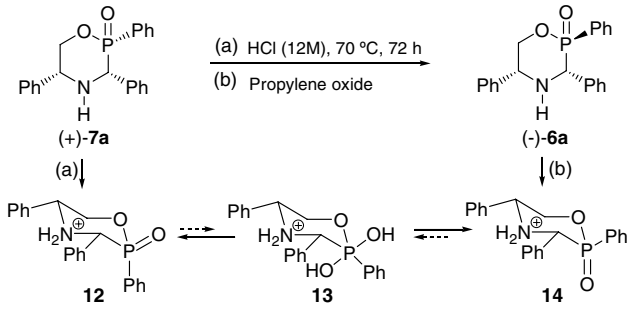
For compound **8**, proton NMR spectra allowed us to confirm the configuration of the two stereogenic centers. All the coupling constants were compatible with the conformation issued from X-ray data analysis.

Similar values were found for the others structures **7a**–**e**, and are listed in Table 2.

Table 2. Coupling constants of 2-aryl-1,4,2-oxazaphosphinanes **7a**–**e**

	Compound				
	7a	**7b**	**7c**	**7d**	**7e**
$^2J_{PHd}$	−19.0	−19.0	−19.0	−19.0	−19.2
$^3J_{PHa}$	18.5	18.6	19.5	18.2	19.8
$^3J_{PHb}$	2.0	2.1	1.3	2.5	0.5
$^3J_{HaHc}$	3.0	3.3	3.7	3.4	3.6
$^3J_{HbHc}$	10.7	10.5	10.2	10.5	10.2

The final step involved the treatment of compound (+)-**7a** with hydrochloric acid solution (35%), which was carried out at 70 °C leading to a clean inversion of configuration at the phosphorus atom (Scheme 4). The reaction was complete after 72 h. Oxazaphosphinane **14** was formed in more than 97% and less than 3% of the starting material **7a** (Table 3). This mechanism probably involved the formation of unstable dihydroxyphosphorane **13** showing two hydroxyl groups in an apical position (Scheme 4). The dynamic equilibrium between the two isomers **12** and **14** favored the thermodynamic product **14**, where all the phenyl substituents were in equatorial positions. Neutralization of ammonium salt **14** by treatment with propylene oxide gave after filtration, pure oxazaphosphinane **6a**. Similarly, the other enantiomer (+)-**7a** gave the same results. Compound **7e** required more drastic conditions and the inversion of configuration took place at 90 °C leading to (2*R*,3*R*,5*R*)-(−)-oxazaphosphinane **6e**. This is consistent with the proposed mechanism, where the initial protonation of the phosphoryl group was slowed down by the electron withdrawing and negative inductive effects caused by the two fluorine atoms on the aromatic substituent. This would prevent the formation of phosphorane **13** and therefore the inversion process (Table 4).



Scheme 4. Inversion of configuration at the phosphorus of 2-aryl-2-oxo-1,4,2-oxazaphosphinanes **7**.

Table 3. Configuration inversion of 2-aryl-1,4,2-oxazaphosphinanes **7**

Reagent compound	Final product compound	Yield (%)[a]
(+)-**7a**	(−)-**6a**	80
(−)-**7a**	(+)-**6a**	88
(+)-**7e**	(−)-**6e**[b]	64

[a] After treatment with propylene oxide.
[b] 48 h to 90 °C.

Table 4. Coupling constants of 2-aryl-[1,4,2]-oxazaphosphinanes **6a** and **6e**

Compound	$^2J_{PHd}$	$^3J_{PHa}$	$^3J_{PHb}$	$^3J_{HaHc}$	$^3J_{HbHc}$
6a	0.0	18.8	2.8	2.6	10.9
6e	0.0	18.8	3.0	2.5	10.9

Suitable crystals for X-ray analysis were obtained from dimethylsulfoxide–methanol solution for compound (+)-**6a**, the absolute configuration of which is shown in Figure 5.[8c]

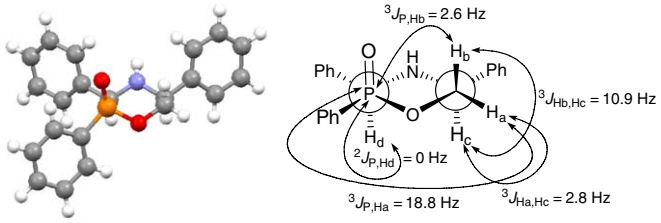


Figure 5. X-ray structure and ^{1}H NMR analysis of (+)-**6a**.

In solution, $^{2}J_{PHd}$ coupling constants were deeply affected by the inversion of configuration at the phosphorus atom changing from −19 to 0.0 Hz while other coupling constants did not change.

3. Conclusion

In conclusion, a sequence involving an arylation reaction and a selective inversion of configuration at the phosphorus atom was shown to be synthetically useful for obtaining phosphinyl analogues of hydroxybupropion with various substituents on aryl directly linked to the phosphorus. Oxazaphosphinanes (+)-**6a** and (−)-**6a** and **6e** were obtained stereoselectively under thermodynamic control, which was consistent with the active hemiketal configuration of hydroxybupropion. We plan to use this methodology in order to prepare the exact phosphorus analogue of *C*-arylmorpholinol **3**.

4. Experimental

All reactions involving air or moisture sensitive reagents or intermediates were carried out under dry nitrogen in flame-dried glassware. Reagents, such as benzaldehyde or aryl iodides were all purified by distillation or sublimation. Solvents were all dried by distillation and stored under nitrogen atmosphere before use, tetrahydrofuran and toluene over sodium wires/benzophenone and dichloromethane over phosphorus pentoxide. Commercially available reagents were used without further purification. Merck silica gel (35–70 μm) was used for column chromatography. Melting points were measured on a Büchi B-540 apparatus and are uncorrected. ^{31}P and ^{19}F spectrums were performed on a Bruker AC 200 MHz spectrometer operating, respectively, at 81 and 188 MHz. ^{1}H and ^{13}C experiments were recorded on Bruker DRX 400 MHz spectrometers with frequency of 101 MHz for ^{13}C. Infrared spectra were recorded on a FT-NICOLET 210 spectrometer. High resolution mass spectra were measured on JEOL JMS-SX 102A spectrometer with *m*-nitrobenzyl alcohol as matrix (NBA) and optical rotation values, with Perkin–Elmer model 241 polarimeter.

4.1. Preparation of (*R*)-(+)- and (*S*)-(−)-2-(benzylidene-amino)-2-phenylethanol (10)

In a 1.0 L flask and under nitrogen, was charged (*S*)- or (*R*)-2-amino-1-phenylethanol (25.0 g, 0.18 mol), followed by dichloromethane (400 mL), benzaldehyde (20.4 mL, 0.2 mol), and sodium sulfate (250 g). After 24 h of strong stirring at ambient temperature, the mixture was filtered on a coarse fritted filter and the residue washed with dichloromethane (200 mL). The solution was concentrated under reduced pressure to afford a pale yellow oil, which solidifies on standing, 34.0 g (83%).

(*R*)- and (*S*)-**10**: mp = 70–71 °C (lit.[12] mp = 78 °C). ^{1}H NMR ($CDCl_3$): Major (open form 87%) δ 2.7 (1H, s broad, N*H*), 3.80 (1H, dd, $^{2}J_{HH} = 11.3$ Hz, $^{3}J_{HH} = 4.1$ Hz, CH_2–O), 3.91 (1H, dd, $^{2}J_{HH} = 11.3$ Hz, $^{3}J_{HH} = 8.7$ Hz, CH_2–O), 4.40 (1H, dd, $^{3}J_{HH} = 8.6$ Hz, $^{3}J_{HH} = 4.3$ Hz, CH_2–C*H*–N), 7.1–7.7 (9H, m, C*H*ar), 8.23 (1H, s, N–C*H*–Ph). Minor (isoxazoline form 13%, two diastereoisomers 60:40) δ 2.7 (1H, s broad, N*H*), 3.71 (0.4H, dd, $^{3}J_{HH} = 8.1$ Hz, $^{2}J_{HH} = 6.8$ Hz, CH_2–O), 3.77 (0.6H, dd, $^{3}J_{HH} = 7.7$ Hz, $^{2}J_{HH} = 7.6$ Hz, CH_2–O), 4.22 (0.6H, dd, $^{3}J_{HH} = 7.7$ Hz, $^{2}J_{HH} = 7.6$ Hz, CH_2–O), 4.31 (0.4H, dd, $^{3}J_{HH} = 8.3$ Hz, $^{2}J_{HH} = 6.8$ Hz, CH_2–O), 4.42 (0.4H, dd, $^{3}J_{HH} = 8.3$ Hz, $^{3}J_{HH} = 8.1$ Hz, CH_2–C*H*–N), 4.44 (0.6H, dd, $^{3}J_{HH} = 7.7$ Hz, $^{3}J_{HH} = 7.6$ Hz, CH_2–C*H*–N), 5.50 (0.6H, s, N–C*H*–Ph), 5.56 (0.4H, s, N–C*H*–Ph), 7.1–7.7 (10H, m, C*H*ar). ^{13}C NMR ($CDCl_3$): Major δ 67.81 (s, *C*H_2–O), 76.27 (s, Ph–*C*H–N), 126.14–131.03 (m, *C*Har), 135.88 (s, *C*ar), 140.68 (s, *C*ar). Minor (isoxazoline form, two diastereoisomers) δ 60.80 (s, CH_2–*C*H–N), 63.01 (s, CH_2–*C*H–N), 72.16 (s, *C*H_2–O), 76.67 (s, *C*H_2–O), 92.62 (s, O–*C*H–N), 93.43 (s, O–*C*H–N), 126–150 (*C*ar and *C*Har). IR (ν/cm^{-1}) 3255, 3077, 3063, 3028, 2944, 2885, 1637, 1600, 1578, 1490, 1453, 1385, 1352, 1306, 1215, 1156, 1134, 1094, 1071, 1055, 1045, 1027.

4.2. Preparation of (2*R*,3*S*,5*S*)-(+)- and (2*S*,3*R*,5*R*)-(−)-3,5-diphenyl-2-hydrogeno-2-oxo-[1,4,2]-oxazaphosphinane (8)

In a 50 mL flask containing the reaction mixture of methyl hypophosphite[8] freshly prepared (55 mmol) under nitrogen were added dry THF (12.5 mL) and (*S*)- or (*R*)-2-benzylidene-amino-2-phenylethanol (12.8 g, 57 mmol). After 24 h at room temperature, sublimed *t*-BuOK (0.7 g, 7 mmol) was added at −5 °C. The reaction mixture was then stirred for 2 h and allowed to stand at room temperature overnight. The solution was evaporated and the residue purified by column chromatography on silica gel with dichloromethane/ethyl acetate (100/0 to 20/80) as eluent, leading to a white solid obtained in 28% yield (4.4 g).

(2*R*,3*S*,5*S*)-**8**: mp = 143–144 °C, $[\alpha]_D^{20} = +19.5$ (*c* 1.04, $CHCl_3$); (2*S*,3*R*,5*R*)-**8**: mp = 143–144 °C, $[\alpha]_D^{20} = -19.0$ (*c* 1.04, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ 33.1 (s); ^{1}H NMR ($CDCl_3$): δ 2.14 (1H, d broad, $^{3}J_{PH} = 35.6$ Hz, N*H*), 4.1–4.4 (4H, m), 6.75 (1H, dd, $^{1}J_{PH} = 553.9$ Hz, $^{3}J_{HH} = 5.0$ Hz, P(O)*H*), 7.21–7.37 (6H, m, C*H*ar), 7.38–7.53 (4H, m, C*H*ar). ^{1}H NMR (CD_3COCD_3): δ 2.14 (1H, d broad, $^{3}J_{PH} = 35.6$ Hz, N*H*), 4.28 (1H, ddd, $^{3}J_{PH} = 21.7$ Hz, $^{2}J_{HH} = 10.8$ Hz, $^{3}J_{HH} = 2.1$ Hz, CH_2–O), 4.34 (1H, dd, $^{2}J_{PH} = 15.4$ Hz, $^{3}J_{HH} = 5.0$ Hz, N–C*H*–Ph), 4.36 (1H, ddd, $^{2}J_{HH} = 10.8$ Hz, $^{3}J_{HH} = 10.5$ Hz, $^{3}J_{PH} = 3.6$ Hz, CH_2–O), 4.42 (1H, ddd, $^{3}J_{HH} = 10.5$ Hz, $^{3}J_{PH} = 2.3$ Hz, $^{3}J_{HH} = 2.1$ Hz, CH_2–C*H*–NH), 6.77 (1H, dd, $^{1}J_{PH} = 553.9$ Hz, $^{3}J_{HH} = 5.0$ Hz, P(O)*H*), 7.3–7.5 (6H, m, C*H*ar), 7.5–7.7 (4H, m, C*H*ar). ^{13}C NMR ($CDCl_3$): δ 61.12 (s, CH_2–*C*H–N), 62.69 (d, $^{1}J_{PC} = 95.9$ Hz, N–*C*H–Ph), 74.92 (d, $^{2}J_{PC} = 8.0$ Hz, O–*C*H_2), 127.32 (s, *C*Har), 127.58 (d, $^{3}J_{PC} = 5.9$ Hz, *C*Har), 128.85 (d, $^{5}J_{PC} = 3.7$ Hz, *C*Har), 128.97 (s, *C*Har), 129.04 (s, *C*Har), 129.13 (d, $^{4}J_{PC} = 2.9$ Hz, *C*Har), 133.37 (d, $^{2}J_{PC} = 5.9$ Hz, *C*ar), 136.98 (s, *C*ar). IR (ν/cm^{-1}) 3481, 3267, 3087, 3057, 3029, 2989, 2919, 2871, 2829, 2788, 2339, 1602, 1584, 1492, 1451, 1358, 1318, 1250, 1204, 1183, 1134, 1084, 1055, 1010. HRMS (FAB$^+$) MH$^+$ calcd for (2*R*,3*S*,5*S*)-$C_{15}H_{17}NO_2P$: 274.0997; found 274.0992. HRMS (FAB$^+$) MH$^+$ calcd for (2*S*,3*R*,5*R*)-$C_{15}H_{17}NO_2P$: 274.0997; found 274.1002.

4.3. General procedure for the preparation of 2-aryl-3,5-diphenyl-2-oxo-[1,4,2]-oxazaphosphinane (7a–e)

In a 25 mL Schlenk tube containing (2*R*,3*S*,5*S*)-(+)- or (2*S*,3*R*,5*R*)-(−)-2-hydrogeno-2-oxo-[1,4,2]-oxazaphosphinane **8** (1.0 g, 3.6 mmol) under N_2 and at room temperature were successively added, toluene (8 mL), triethylamine (1.1 g, 1.6 mL, 10.8 mmol), aryl iodide, or bromide (3.6 mmol) and palladium tetrakis(triphenyl)phosphine (0.42 g, 0.36 mmol). The reaction mixture was stirred and heated at 90 °C for 4 h. After cooling, the mixture was concentrated under vacuum and the crude residue purified by a column chromatography on silica gel with dichloromethane/ethyl acetate as eluent (gradient 90/10 to 70/30). A white solid was obtained.

4.3.1. 2,3,5-Triphenyl-2-oxo-[1,4,2]-oxazaphosphinane ((2*R*,3*S*,5*S*)-7a).

70%, mp = 131–133 °C, $[\alpha]_D^{20} = -138.5$ (*c* 0.52, $CHCl_3$); (2*S*,3*R*,5*R*)-**7a**: 74%, mp = 132–134 °C, $[\alpha]_D^{20} = +140.3$ (*c* 0.52, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ 28.7 (s). ^1H NMR ($CDCl_3$): δ 2.32 (1H, d broad, $^3J_{PH} = 30.9$ Hz, N*H*), 4.42 (1H, ddd, $^3J_{PH} = 18.5$ Hz, $^2J_{HH} = 10.9$ Hz, $^3J_{HH} = 3.0$ Hz, CH_2–O), 4.50 (1H, ddd, $^2J_{HH} = 10.9$ Hz, $^3J_{HH} = 10.7$ Hz, $^3J_{PH} = 2.0$ Hz, CH_2–O), 4.57 (1H, dd, $^3J_{HH} = 10.7$ Hz, $^3J_{HH} = 3.0$ Hz, CH$_2$–C*H*–N), 4.80 (1H, d, $^2J_{PH} = 19.0$ Hz, N–C*H*–Ph), 7.1–7.6 (13H, m, C*Har*), 7.8–7.9 (2H, m, C*Har*). ^{13}C NMR ($CDCl_3$): δ 62.44 (d, $^3J_{PC} = 2.2$ Hz, CH$_2$–*C*H–NH), 65.07 (d, $^1J_{PC} = 98.1$ Hz, N–*C*H–Ph), 75.07 (d, $^2J_{PC} = 8.0$ Hz, *C*H$_2$–O), 127.25 (d, $^3J_{PC} = 5.1$ Hz, *C*Har), 127.37 (s, *C*Har), 127.8–128.0 (m, *C*Har), 127.8–128.1 (m, *C*Har), 128.10 (d, $^1J_{PC} = 125.9$ Hz, *C*ar), 128.4–129.1 (m, *C*Har), 132.2–132.4 (m, *C*Har), 134.53 (d, $^2J_{PC} = 5.8$ Hz, *C*ar), 137.62 (s, *C*ar). IR (ν/cm^{-1}) 3449, 3279, 3061, 3029, 2981, 2919, 2942, 2878, 2812, 1601, 1591, 1491, 1452, 1436, 1242, 1204, 1192, 1120, 1083, 1055, 1017. HRMS (FAB$^+$) MH$^+$ calcd for (2*R*,3*S*,5*S*)-$C_{21}H_{21}NO_2P$: 350.1310; found 350.1311; HRMS (FAB$^+$) MH$^+$ calcd for (2*S*,3*R*,5*R*)-$C_{21}H_{21}NO_2P$: 350.1310; found 350.1320.

4.3.2. 2-*p*-Methoxyphenyl-3,5-diphenyl-2-oxo-[1,4,2]-oxazaphosphinane ((2*R*,3*S*,5*S*)-7b).

75%, mp = 200–201 °C, $[\alpha]_D^{20} = -145.0$ (*c* 0.51, $CHCl_3$); (2*S*,3*R*,5*R*)-**7b**: 73%, mp = 200–201 °C, $[\alpha]_D^{20} = +145.6$ (*c* 0.51, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ 29.17 (s). ^1H NMR ($CDCl_3$): δ 2.29 (1H, d broad, $^3J_{PH} = 30.3$ Hz, N*H*), 4.38 (1H, ddd, $^3J_{PH} = 18.6$ Hz, $^2J_{HH} = 11.1$ Hz, $^3J_{HH} = 3.3$ Hz, CH_2–O), 4.46 (1H, ddd, $^2J_{HH} = 11.1$ Hz, $^3J_{HH} = 10.5$ Hz, $^3J_{PH} = 2.1$ Hz, CH_2–O), 4.54 (1H, dd, $^3J_{HH} = 10.5$ Hz, $^3J_{HH} = 3.3$ Hz, CH$_2$–C*H*–N), 4.75 (1H, d, $^2J_{PH} = 19.0$ Hz, N–C*H*–Ph), 6.8–6.9 (2H, m, C*Har*), 7.1–7.3 (3H, m, C*Har*), 7.3–7.5 (5H, m, C*Har*), 7.5–7.6 (2H, m, C*Har*), 7.7–7.9 (2H, m, C*Har*). ^{13}C NMR ($CDCl_3$): δ 55.23 (s, O–*C*H$_3$), 62.42 (d, $^3J_{PC} = 1.5$ Hz, CH$_2$–*C*H–N), 65.06 (d, $^1J_{PC} = 98.8$ Hz, N–*C*H–Ph), 74.87 (d, $^2J_{PC} = 6.6$ Hz, *C*H$_2$–O), 113.56 (d, $^3J_{PC} = 13.9$ Hz, *C*Har), 119.34 (d, $^1J_{PC} = 131.7$ Hz, *C*ar), 127.24 (d, $^3J_{PC} = 5.1$ Hz, *C*Har), 127.33 (s, *C*Har), 127.79 (d, $^5J_{PC} = 2.9$ Hz, *C*Har), 128.40 (d, $^4J_{PC} = 2.9$ Hz, *C*Har), 128.82 (s, *C*Har), 129.02 (s, *C*Har), 134.20 (d, $^2J_{PC} = 10.3$ Hz, *C*Har), 134.84 (d, $^2J_{PC} = 5.9$ Hz, *C*ar), 137.83 (s, *C*ar), 162.71 (s, *C*ar). IR (ν/cm^{-1}) 3453, 3283, 3087, 3059, 3032, 2971, 2939, 2884, 2836, 2808, 1599, 1568, 1502, 1494, 1455, 1436, 1294, 1235, 1182, 1119, 1084, 1053, 1028, 1016. HRMS (FAB$^+$) MH$^+$ calcd for (2*R*,3*S*,5*S*)-$C_{22}H_{23}NO_3P$: 380.1416; found 380.1428; HRMS (FAB$^+$) MH$^+$ calcd for (2*S*,3*R*,5*R*)-$C_{22}H_{23}NO_3P$: 380.1416; found 380.1414.

4.3.3. 2-*p*-Bromophenyl-3,5-diphenyl-2-oxo-[1,4,2]-oxazaphosphinane ((2*R*,3*S*,5*S*)-7c).

69%, mp = 169–170 °C, $[\alpha]_D^{20} = -160.4$ (*c* 0.51, $CHCl_3$); (2*S*,3*R*,5*R*)-**7c**: 68%, mp = 169–170 °C, $[\alpha]_D^{20} = +160.8$ (*c* 0.51, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ 28.0 (s). ^1H NMR ($CDCl_3$): δ 2.36 (1H, d broad, $^3J_{PH} = 23.1$ Hz, N*H*), 4.42 (1H, ddd, $^3J_{PH} = 19.5$ Hz, $^2J_{HH} = 11.2$ Hz, $^3J_{HH} = 3.7$ Hz, CH_2–O), 4.44 (1H, ddd, $^2J_{HH} = 11.2$ Hz, $^3J_{HH} = 10.2$ Hz, $^3J_{PH} = 1.3$ Hz, CH_2–O), 4.57 (1H, dd, $^3J_{HH} = 10.2$ Hz, $^3J_{HH} = 3.7$ Hz, CH$_2$–C*H*–N), 4.79 (1H, d, $^2J_{PH} = 19.0$ Hz, N–C*H*–Ph), 7.2–7.3 (3H, m, C*Har*), 7.3–7.6 (9H, m, C*Har*), 7.6–7.8 (2H, m, C*Har*). ^{13}C NMR ($CDCl_3$): δ 62.39 (d, $^3J_{PC} = 1.5$ Hz, CH$_2$–*C*H–N), 64.86 (d, $^1J_{PC} = 99.5$ Hz, N–*C*H–Ph), 75.20 (d, $^2J_{PC} = 8.0$ Hz, *C*H$_2$–O), 127.11 (d, $^3J_{PC} = 5.1$ Hz, *C*Har), 127.16 (d, $^1J_{PC} = 126.6$ Hz, *C*ar), 127.30 (s, *C*Har), 127.65 (d, $^4J_{PC} = 3.7$ Hz, *C*ar), 128.06 (d, $^5J_{PC} = 2.9$ Hz, *C*Har), 128.59 (d, $^4J_{PC} = 2.9$ Hz, *C*Har), 128.99 (s, *C*Har), 129.11 (s, *C*Har), 131.32 (d, $^3J_{PC} = 13.2$ Hz, *C*Har), 133.73 (d, $^2J_{PC} = 9.5$ Hz, *C*Har), 134.19 (d, $^2J_{PC} = 5.1$ Hz, *C*ar), 137.44 (s, *C*ar). IR (ν/cm^{-1}) 3436, 3264, 3087, 3063, 3028, 2976, 2897, 1602, 1576, 1502, 1497, 1479, 1455, 1228, 1210, 1174, 1119, 1120, 1053, 1068, 1019, 1008. HRMS (FAB$^+$) MH$^+$ calcd for (2*R*,3*S*,5*S*)-$C_{21}H_{20}{}^{79}BrNO_2P$: 428.0415; found 428.0392; HRMS (FAB$^+$) MH$^+$ calcd for (2*S*,3*R*,5*R*)-$C_{21}H_{20}{}^{79}BrNO_2P$: 428.0415; found 428.0424.

4.3.4. 2-*m*-Chlorophenyl-3,5-diphenyl-2-oxo-[1,4,2]-oxazaphosphinane ((2*R*,3*S*,5*S*)-7d).

72%, mp = 128–130 °C, $[\alpha]_D^{20} = -152.8$ (*c* 0.55, $CHCl_3$); (2*S*,3*R*,5*R*)-**7d**: 73%, mp = 128–130 °C, $[\alpha]_D^{20} = +152.7$ (*c* 0.55, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ 26.9 (s). ^1H NMR ($CDCl_3$): δ 2.48 (1H, s broad, N*H*), 4.44 (1H, ddd, $^3J_{PH} = 18.2$ Hz, $^2J_{HH} = 11.0$ Hz, $^3J_{HH} = 3.4$ Hz, CH_2–O), 4.50 (1H, ddd, $^2J_{HH} = 11.0$ Hz, $^3J_{HH} = 10.5$ Hz, $^3J_{PH} = 2.5$ Hz, CH_2–O), 4.57 (1H, dd, $^3J_{HH} = 10.5$ Hz, $^3J_{HH} = 3.4$ Hz, CH$_2$–C*H*–N), 4.80 (1H, d, $^2J_{PH} = 19.0$ Hz, N–C*H*–Ph), 7.2–7.5 (10H, m, C*Har*), 7.5–7.6 (2H, m, C*Har*), 7.6–7.9 (2H, m, C*Har*). ^{13}C NMR ($CDCl_3$): δ 62.39 (d, $^3J_{PC} = 2.2$ Hz, CH$_2$–*C*H–N), 64.96 (d, $^1J_{PC} = 99.5$ Hz, N–*C*H–Ph), 75.19 (d, $^2J_{PC} = 8.0$ Hz, *C*H$_2$–O), 127.17 (d, $^3J_{PC} = 5.1$ Hz, *C*Har), 127.35 (s, *C*Har), 128.14 (d, $^5J_{PC} = 3.7$ Hz, *C*Har), 128.59 (d, $^3J_{PC} = 2.9$ Hz, *C*Har), 129.02 (s, *C*Har), 129.13 (s, *C*Har), 129.40 (d, $^3J_{PC} = 14.6$ Hz, *C*Har), 130.23 (d, $^1J_{PC} = 123.7$ Hz, *C*ar), 133.30 (d, $^2J_{PC} = 8.8$ Hz, *C*Har), 132.24 (d, $^2J_{PC} = 9.5$ Hz, *C*ar), 132.48 (d, $^4J_{PC} = 2.9$ Hz, *C*Har), 134.00 (d, $^2J_{PC} = 5.1$ Hz, *C*ar), 134.28 (d, $^3J_{PC} = 16.8$ Hz, *C*ar), 137.27 (s, *C*ar). IR (ν/cm^{-1}) 3444, 3278, 3056, 3029, 2981, 2944, 2882, 2816, 1601, 1563, 1494, 1470, 1453, 1431, 1395, 1373, 1320, 1241, 1210, 1192, 1131, 1082, 1055, 1028, 1016. HRMS (FAB$^+$) MH$^+$ calcd for (2*R*,3*S*,5*S*)-$C_{21}H_{20}{}^{35}ClNO_2P$: 384.0920; found 384.0929; HRMS (FAB$^+$) MH$^+$ calcd for (2*S*,3*R*,5*R*)-$C_{21}H_{20}{}^{35}ClNO_2P$: 384.0920; found 384.0919.

4.3.5. 2-(3,5-Difluorophenyl)-3,5-diphenyl-2-oxo-[1,4,2]-oxazaphosphinane ((2*R*,3*S*,5*S*)-7e). 64%, mp = 138–140 °C, $[\alpha]_D^{20} = -122.2$ (*c* 0.54, $CHCl_3$); (2*S*,3*R*,5*R*)-**7e**: 69%, mp = 138–140 °C, $[\alpha]_D^{20} = +122.2$ (*c* 0.54, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ 25.2 (t, $^4J_{PF} = 7.1$ Hz). ^{19}F NMR ($CDCl_3$): δ 25.2 (t, $^4J_{PF} = 7.2$ Hz). ^1H NMR ($CDCl_3$): δ 2.46 (1H, d broad, N*H*), 4.44 (1H, ddd, $^3J_{PH} = 19.8$ Hz, $^2J_{HH} = 11.3$ Hz, $^3J_{HH} = 3.6$ Hz, C*H*$_2$–O), 4.46 (1H, ddd, $^2J_{HH} = 11.3$ Hz, $^3J_{HH} = 10.2$ Hz, $^3J_{PH} = 0.5$ Hz, C*H*$_2$–O), 4.56 (1H, dd, $^3J_{HH} = 10.2$ Hz, $^3J_{HH} = 3.6$ Hz, CH$_2$–C*H*–N), 4.81 (1H, d, $^2J_{PH} = 19.2$ Hz, N–C*H*–Ph), 6.8–6.9 (1H, m, C*H*ar), 7.2–7.3 (3H, m, C*H*ar), 7.4–7.5 (7H, m, C*H*ar), 7.5–7.6 (2H, m, C*H*ar). ^{13}C NMR ($CDCl_3$): δ 62.42 (d, $^3J_{PC} = 2.2$ Hz, CH$_2$–*C*H–N), 64.76 (d, $^1J_{PC} = 101.0$ Hz, N–*C*H–Ph), 75.35 (d, $^2J_{PC} = 8.8$ Hz, *C*H$_2$–O), 108.02 (td, $^2J_{FC} = 24.9$ Hz, $^4J_{PC} = 1.5$ Hz), 115.24 (m, *C*Har), 127.04 (d, $^3J_{PC} = 4.4$ Hz, *C*Har), 127.32 (s, *C*Har), 128.28 (d, $^5J_{PC} = 3.7$ Hz, *C*Har), 128.69 (d, $^4J_{PC} = 3.7$ Hz, *C*Har), 129.13 (s, *C*Har), 129.20 (s, *C*Har), 131.97 (dt, $^1J_{PC} = 124.4$ Hz, $^3J_{FC} = 7.3$ Hz, *C*ar), 133.64 (d, $^2J_{PC} = 5.9$ Hz, *C*ar), 137.04 (s, *C*ar), 162.49 (ddd, $^1J_{FC} = 252.5$ Hz, $^4J_{FC} = 21.2$ Hz, $^4J_{PC} = 11.0$ Hz). IR (ν/cm^{-1}) 3280, 3092, 3060, 3038, 2985, 2949, 2886, 2824, 1613, 1596, 1495, 1454, 1422, 1298, 1122, 1106, 1056, 1081, 1019. HRMS (FAB$^+$) MH$^+$ calcd for (2*R*,3*S*,5*S*)-$C_{21}H_{19}F_2NO_2P$: 384.1121; found 386.1130; HRMS (FAB$^+$) MH$^+$ calcd for (2*S*,3*R*,5*R*)-$C_{21}H_{19}F_2NO_2P$: 386.1121; found 386.1114.

4.4. General procedure for the inversion of configuration reaction

In a 50 mL Schlenk tube, 2-aryl-[1,4,2]-oxazaphosphinane (0.75 g) (−)-**7a**, (+)-**7a**, or (+)-**7e** was mixed with a concentrated solution of hydrochloric acid (25 mL, 12 M) at 70 °C (90 °C for **7e**). After 72 h (48 h for **7e**), the reaction mixture was cooled at room temperature, and diluted with a saturated brine solution (25 mL), filtered on a coarse fritted filter and the cake washed with brine (2 × 25 mL). After drying, the amorphous solid was treated with propylene oxide (100 mL) for 24 h. The crude mixture was filtered and the solution evaporated, with a white solid being obtained.

4.4.1. 2,3,5-Triphenyl-2-oxo-[1,4,2]-oxazaphosphinane ((2*S*,3*S*,5*S*)-6a). 88%, mp >250 °C, $[\alpha]_D^{20} = +91.1$ (*c* 0.48, $CHCl_3$); (2*R*,3*R*,5*R*)-**6a**: 80%, mp >250 °C, $[\alpha]_D^{20} = -91.7$ (*c* 0.48, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ 29.0 (s). ^1H NMR ($CDCl_3$): δ 2.35 (1H, s broad, N*H*), 4.29 (1H, ddd, $^2J_{HH} = 11.1$ Hz, $^3J_{HH} = 2.8$ Hz, $^3J_{PH} = 18.8$ Hz, C*H*$_2$–O), 4.46 (1H, s, N–C*H*–Ph), 4.57 (1H, dd, $^3J_{HH} = 10.9$ Hz, $^3J_{HH} = 2.8$ Hz, CH$_2$–C*H*–N), 4.80 (1H, ddd, $^2J_{HH} = 11.1$ Hz, $^3J_{HH} = 10.9$ Hz, $^3J_{PH} = 2.6$ Hz, C*H*$_2$–O), 7.2–7.5 (10H, m, C*H*ar), 7.5–7.6 (3H, m, C*H*ar), 7.7–7.9 (2H, m, C*H*ar). ^{13}C NMR ($CDCl_3$): δ 62.83 (s, CH$_2$–*C*H–N), 64.28 (d, $^1J_{PC} = 97.3$ Hz, N–*C*H–Ph), 71.07 (d, $^2J_{PC} = 5.9$ Hz, *C*H$_2$–O), 129–127 (m, *C*Har and *C*ar), 132.25 (d, $^2J_{PC} = 9.5$ Hz, *C*Har), 132.93 (d, $^4J_{PC} = 2.2$ Hz, *C*Har), 135.23 (d, $^2J_{PC} = 4.4$ Hz, *C*ar), 137.94 (s, *C*ar). IR (ν/cm^{-1}) 3444, 3306, 3061, 3083, 3065, 3031, 2938, 2886, 2859, 1601, 1591, 1491, 1454, 1439, 1233, 1216, 1125, 1080, 1043, 1027. HRMS (FAB$^+$) MH$^+$ calcd for (2*S*,3*S*,5*S*)-$C_{21}H_{21}NO_2P$: 350.1310; found 350.1317; HRMS (FAB$^+$) MH$^+$ calcd for (2*R*,3*R*,5*R*)-$C_{21}H_{21}NO_2P$: 350.1310; found 350.1313.

4.4.2. 2-(3,5-Difluoro)phenyl-3,5-diphenyl-2-oxo-[1,4,2]-oxazaphosphinane ((2*R*,3*R*,5*R*)-6e). 64%, mp = 196–197 °C, $[\alpha]_D^{20} = -80.0$ (*c* 0.50, acetone). ^{31}P NMR ($CDCl_3$): δ 26.29 (s). ^1H NMR (CD_3COCD_3): δ 2.86 (1H, s broad, N*H*), 4.21 (1H, ddd, $^2J_{HH} = 10.9$ Hz, $^3J_{HH} = 3.0$ Hz, $^3J_{PH} = 18.7$ Hz, C*H*$_2$–O), 4.42 (1H, td, $^3J_{HH} = 10.9$ Hz, $^3J_{HH} = 2.5$ Hz, C*H*$_2$–O), 4.59 (1H, dd, $^3J_{HH} = 10.9$ Hz, $^3J_{HH} = 3.0$ Hz, CH$_2$–C*H*–N), 4.60 (1H, s, N–C*H*–Ph), 7.1–7.3 (11H, m, C*H*ar), 7.4–7.5 (2H, m, C*H*ar). ^{13}C NMR (CD_3COCD_3): δ 62.66 (s, CH$_2$–*C*H–N), 64.10 (d, $^1J_{PC} = 99.5$ Hz, N–*C*H–Ph), 72.43 (d, $^2J_{PC} = 5.9$ Hz, *C*H$_2$–O), 109.08 (td, $^2J_{FC} = 25.6$ Hz, $^4J_{PC} = 1.5$ Hz), 116.13 (m, *C*Har), 128.0–130 (m, *C*Har and *C*ar), 134.83 (dt, $^1J_{PC} = 130.3$ Hz, $^3J_{FC} = 7.3$ Hz, *C*ar), 136.77 (d, $^2J_{PC} = 5.1$ Hz, *C*ar), 139.58 (s, *C*ar), 163.53 (ddd, $^1J_{FC} = 251.4$ Hz, $^3J_{FC} = 20.5$ Hz, $^3J_{PC} = 11.0$ Hz). IR (ν/cm^{-1}) 3310, 3072, 3034, 2936, 2863, 1610, 1590, 1493, 1456, 1426, 1304, 1234, 1219, 1128, 1104, 1082. HRMS (FAB$^+$) MH$^+$ calcd for (2*R*,3*R*,5*R*)-$C_{21}H_{19}F_2NO_2P$: 386.1141; found 386.1141.

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