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Enantiomeric 2-Anilino-2-oxo-1,3,2-oxazaphosphorinanes: Synthesis and NMR-Investigation of Their Non-racemic Mixtures

Andrei B.Ouryupin[+], Mikhail I.Kadyko[+], Pavel V.Petrovskii[++] and Erlen I.Fedin[+++*]

Laboratory of Organophosphorus Compounds[+] and Laboratory of NMR-Spectroscopy[++], A.N.Nesmeyanov Institute of Organo-Element Compounds, Russian Academy of Sciences, Vavilova 28, Moscow 117813, Russia

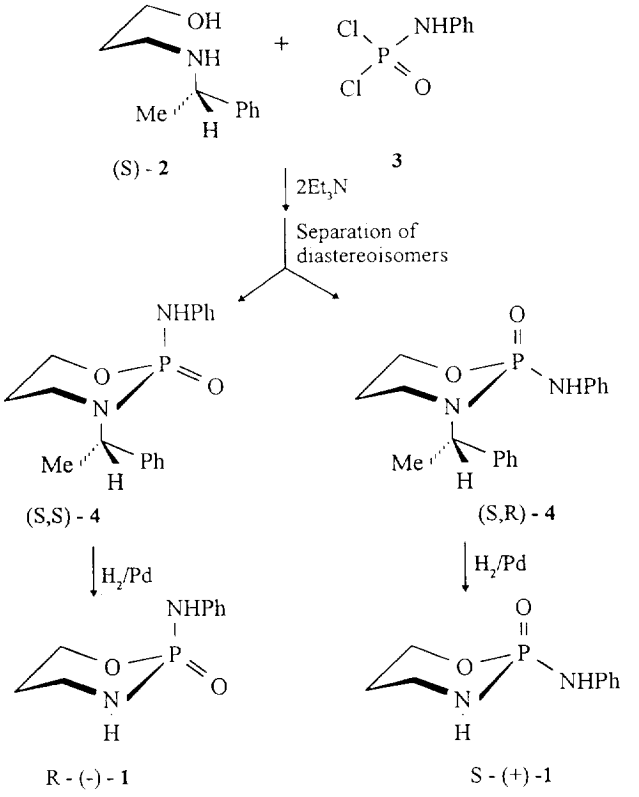
Andrzej Okruszek*, Ryszard Kinas and Wojciech J.Stec

Department of Bioorganic Chemistry, Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland

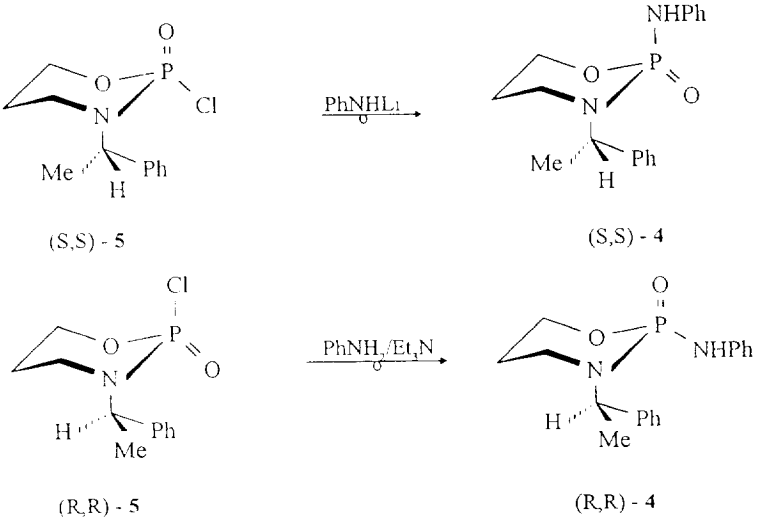
Abstract: Enantiomeric R-(-)- and (S)-(+)-2-anilino-2-oxo-1,3,2-oxazaphosphorinanes **(1)** have been synthesized by catalytic debenzylation of separated diastereomers of 3-(α-methylbenzyl)-2-anilino-2-oxo-1,3,2-oxazaphosphorinanes. Self-induced diastereomeric anisochronicity in non-racemic mixtures of these enantiomers was shown to vary with enantiomeric composition, overall specimen concentration, and temperature. The equilibrium constants of monomer-dimer and homo-cross-associate diastereomeric equilibria are estimated for the first time.

Introduction

So far developed methods of assigment of enantiomeric purity of any chiral molecule are based on the different properties displayed by enantiomeric molecules associated with another chiral agent.[1] In other words, they are based on the principle of formation of dynamic diastereomeric systems. These can be also initiated by the presence of non-equivalent surrounding of each enantiomer in non-racemic mixtures of enantiomers of the same compound. This type of enantiomeric discrimination can be observed in NMR spectra of partially enriched enantiomers under appropriate conditions[2,3] due to the phenomenon of self-induced diastereomeric anisochronism (SIDA), allowing one to determine enantiomeric purity without introduction of chiral auxiliaries or chiral solvents. Under appropriate conditions, solutions of non-racemic mixtures of enantiomers may display separate signals in NMR spectra owing to each enantiomer, and the molar ratios of enantiomers are equal to ratios of intensities of these signals. The signal separation ($\Delta\delta$) appears to be proportional to the difference in enantiomer concentrations.



Scheme 1



Scheme 2

The present work constitutes the continuation of our earlier investigations,[4] concerning the influence of structural motifs on the possibility of observing SIDA. Some phosphoramidates and amino-alcohols, as well as the products of their cyclization, have been found to manifest enantiomer discrimination in ^{1}H and ^{31}P NMR spectra of their non-racemic mixtures. In this report we present in detail our results on SIDA of cyclic 2-anilino-2-oxo-1,3,2-oxazaphosphorinanes.

Results and Discussion

It was shown earlier that the pronounced solute-solute hydrogen-bonding favours the observation of SIDA.[3,4] Uskokovic was first to observe enantiomeric discrimination in ^{1}H NMR spectra of non-racemic mixtures of dihydroquinine[2] and other researchers proved the generality of such discrimination for some phosphorus acids derivatives (including non-cyclic phosphoramidates),[3,5] hydroxy-acids,[6] carboxamides,[7] amino-acids derivatives,[8] aminoalcohols,[4e] diols[9] and thiazepines.[10] It is worth mentioning, that in addition to ^{1}H some other sensor nuclei were used such as ^{31}P and ^{13}C. Use of this technique in analysis is possible due to good separation of signals ($\Delta\delta$) in many cases, and the improved accuracy of signal integration possible with modern NMR spectrometers. Apart from carboxamide and phosphoramide groups, aromatic motifs were found to increase SIDA-effects.[5,11]

Since the possibility of SIDA observation is dependent upon the structure of enantiomers and their ability to aggregate via hydrogen bond formation it was tempting to propose some cyclic phosphoramidates as models for detailed investigation of $\Delta\delta$ occurence under various conditions. Among them, enantiomeric forms of 2-anilino-2-oxo-1,3,2-oxazaphosphorinane (**1**) seemed to be accessible due to the approach developed earlier.[12] Both enantiomers of **1** have been synthesized by the cyclization of N-[(**S**)-α-methylbenzyl]-3-aminopropan-1-ol [(S)-**2**] with N-phenylphosphoramidodichloridate (**3**). The resulting diastereoisomeric phosphoramidates (Sc,Sp+Sc,Rp)-**4** have been separated by column chromatography and subjected to hydrogenolytic debenzylation to give pure enantiomers of **1** (Scheme 1).

The assignment of absolute configuration at phosphorus atom in **1** and **4** was possible by alternative stereospecific synthesis of diastereomers (Rc,Rp)-**4** and (Sc,Sp)-**4** from diastereomerically pure 2-chloro-3-(α-methylbenzyl)-2-oxo-1,3,2-oxazaphosphorinanes of known chirality,[13] (Rc,Rp)-**5** and (Sc,Sp)-**5**, respectively, (Scheme 2). It has been assumed that, like with other N-nucleophiles, the reaction of **5** with aniline proceeds with inversion of configuration at the phosphorus atom.[13] Since the conversion **4**- > **1** occurs without cleavage of bonds to the phosphorus atom, the absolute configuration of (-)-**1** was assigned to be R.

Chloroform or methylene chloride solutions of non-racemic mixtures of R-(-)-**1** and S-(+)-**1** or their precursors (Sc,Sp)-**4** and (Rc,Rp)-**4** displayed differentiated signals in their ^{31}P NMR spectra. The $\Delta\delta$ value was found to depend on temperature and on the relative concentrations of enantiomers. Maximal $\Delta\delta$ values were measured at lower temperatures and for greater enantiomer ratios. Thus, upon constant concentration (c=2 mg/ml), at -50°C, the magnitude of $\Delta\delta$ changes from 0.3 ppm for (R)-**1**/(S)-**1** = 90:10 to 0.08 ppm for (R)-**1**/(S)-**1** = 37.5:62.5.

A representative set of examples of ^{31}P NMR spectra of non-racemic mixtures of (R)-**1** and (S)-**1** is shown in Figure 1. Each of the separate signals present in the spectra corresponds to a single enantiomer of (R)-**1** or (S)-**1** in the non-racemic mixture. The molar ratio of enantiomers was found to correspond to the ratio of intensities of the signals observed in the spectra integrated under low noise conditions.

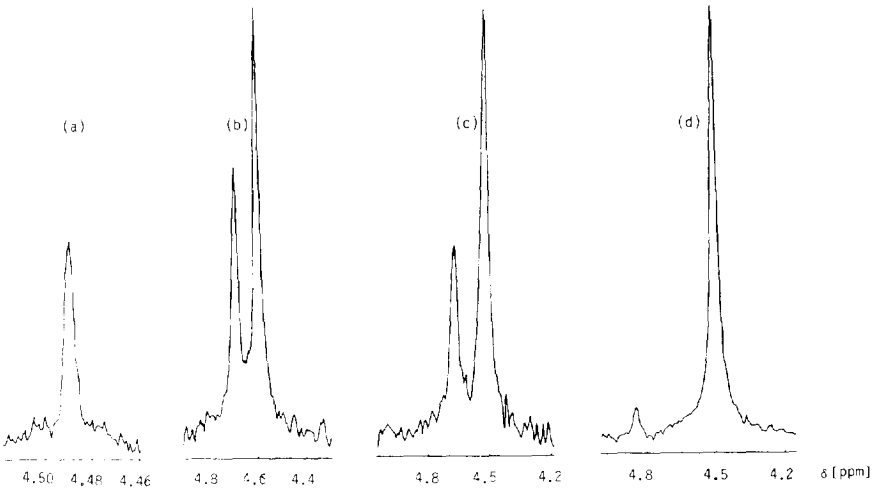


Figure 1. ^{31}P-NMR signals of pure (**R**)-**1** (a) and non-racemic mixtures of (**R**)-**1** and (**S**)-**1** in $CDCl_3$ solution at -50°C: (a) pure (**R**)-**1**; (b) **R/S**= 37.5/62.5; (c) **R/S**=3/1; (d) **R/S**=9/1.

The dependence of the magnitude of $\Delta\delta$ on the temperature was demonstrated for the mixture (R)-**1**/(S)-**1** = 25:75 (Table 1). The chemical shift difference narrows with an increase in temperature, however, the advantage resulting from lowering of the temperature is limited. At the temperatures below -70°C the exchange between associates may be slow enough to cause considerable broadening of the NMR signals and appearance of additional peaks. Nevertheless, experimental data support the presence of SIDA in the sufficiently broad temperature range.

Similar SIDA effect has been found for 1,3,2-oxazaphosphorinane derivatives (Sc,Sp)-**4** and (Rc,Rp)-**4** in the ^{31}P NMR spectra of their non-racemic mixtures. However, in this case the magnitude of $\Delta\delta$ is essentially lower (e.g. 0.1 ppm for the mixture (Sc,Sp)-**4**/(Rc,Rp)-**4** = 9:1) as compared to that observed for **1**. The hydrogen-bonded associations of **4** must be weaker because of participation of only one amidate fragment in the chiral discrimination process.

Table 1. Self-Induced Chemical Shift Nonequivalence ($\Delta\delta$) of ^{31}P sensor nuclei for the 1:3 mixture of (R)-**1** and (S)-**1**[a]

Temp. °C	δ ^{31}P (ppm)[b]		$\Delta\delta$ (ppm)[c]
	(R)-**1**	(S)-**1**	
-20	3.667	3.573	0.094
-30	3.887	3.768	0.119
-40	4.093	3.949	0.144
-50	4.278	4.095	0.183
-60	4.445	4.223	0.222
-70	4.611	4.339	0.272

[a]$CHCl_3$ solution; total concentration $0.94x10^{-2}$ M.
[b]Chemical shifts of individual enantiomers in the mixture.
[c]$\Delta\delta = \delta_R - \delta_S$

In spite of reliability and straightforward interpretation of ^{31}P NMR spectroscopic data, due to larger window of chemical shift values than in the proton spectra, their application for examination of chiral discrimination in solution is inevitably restricted to organophosphorus compounds. In addition, there are some difficulties connected with the spectral references in cases, where either 1% or 85% H_3PO_4 are used as external standards during low temperature measurements. Thus, similar examination of the same non-racemic mixtures of **1** by ^1H NMR spectroscopy has been performed with the aim of comparing the diastereoisomer discrimination in ^{31}P and ^1H NMR spectra. Exocyclic amidate protons were found to be useful sensor nuclei for the study of non-bonding interactions, as was observed for carboxamides.[8] The data presented in Table 2 clearly show that chemical shifts differences for non-racemic mixtures of enantiomers of **1** depend on their composition and on the temperature.It is worth mentioning that under the same conditions the $\Delta\delta$ value for amidate protons (sharp singlets) in ^1H NMR spectra is essentially higher than $\Delta\delta$ for phosphorus nuclei in ^{31}P NMR spectra of the same mixtures. Therefore, the enantiomeric purity of **1** could, alternatively, be estimated by the analysis of their proton spectra. In addition, the effect of SIDA has been shown to occur over a broad temperature range.

The investigation of non-racemic mixtures of (S,S)-**4** and (R,R)-**4** by ^1H NMR spectroscopy has demonstrated the appearance of the SIDA-effect not only for amidate protons, but also for methyl protons of 3-(α-methylbenzyl) group (Table 3). Thus, two groups of protons could be used as sensor nuclei to estimate enantiomeric purity of 1,3,2-oxazaphosphorinanes studied. In spite of small magnitude of $\Delta\delta$, the resolution of signals is quite satisfactory. In addition, the analysis could be accomplished at room temperature. It is also worth mentioning that similar values of $\Delta\delta$ for NH and CH_3 protons were measured at various temperatures with the opposite position of signals related to the enantiomer being the major component of the mixture.

Another parameter which had to be taken into account was the concentration. It was demonstrated, that the overall concentration of specimen in solution influences the possibility of observing SIDA. The concentration dependence of chemical shifts of $CDCl_3$ solutions of pure (R)-**1** and racemic **1** (δ_r) has been measured at various temperatures to determine optimal conditions for enantiomeric analysis (Figure 2). It appeared that under certain conditions of temperature and concentration the deviation δ_r-δ_R becomes negligible, which makes the method useless in such cases. The temperature limit has been described previously[4c] for methanephosphonic acid N,N'-bis-(1-phenylethyl)diamide, where the differentiated signals could be observed between -20° and -30°C only. Similar effects have been observed for the non-racemic mixtures of aminoacid derivatives.[14]

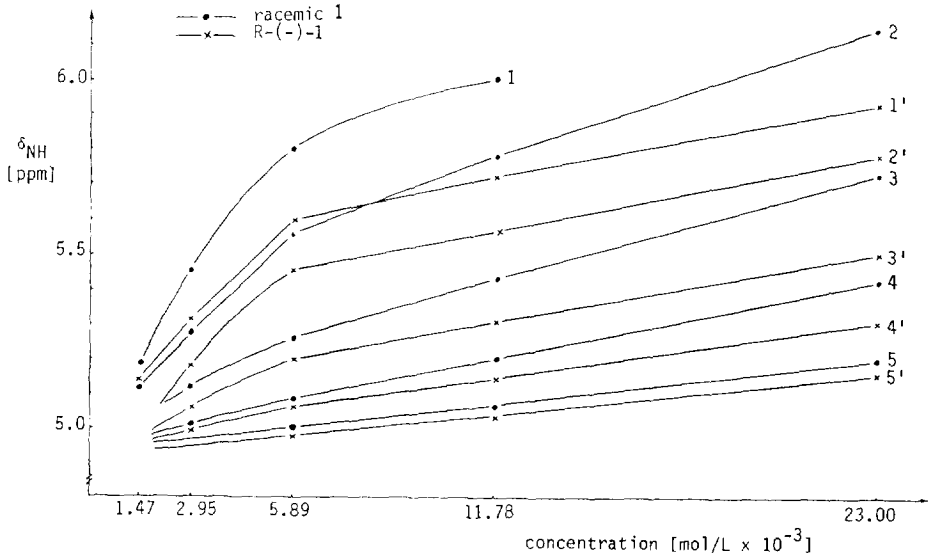


Figure 2. The concentration and temperature dependence of ^{1}H NMR chemical shifts of exocyclic amide protons (NH) for racemic **1** and pure **R-(-)-1** in $CDCl_3$ solution: -30°C (1,1'); -20°C (2,2'); 0°C (3,3'); 20°C (4,4'); 40°C (5,5').

The data listed in Table 2 correspond to linear dependences of δ_R (as well as δ_S) on the relative concentrations of enantiomers at all temperatures except for -30°C. These data, after treatment according to SCADA (Statistically Controlled Associate-Diastereomeric Anisochronism) theory,[3] yield a value of enantioselectivity parameter $m=1$, which means, that there is no preference of homo- or cross-association.[3] Similarly, at -30°C a weak preference of cross-association, (S-R) was revealed. The values of the maximal difference, ($\Delta\delta_{hc}$) between chemical shifts of homo- and cross-associates, extrapolated to enantiomeric excess equal 1, were found to increase progressively with the change of temperature from +30°C to -70°C (see Table 1 and Table 2).

Table 2. Non-equivalent ^{1}H NMR chemical shifts of the exocyclic amide protons for the mixtures of (S)-**1** and (R)-**1**[a]

(S)-**1**/(R)-**1**	δ NH (ppm)											
	(S)-**1**	(R)-**1**	(S)-**1**	(R)-**1**	(S)-**1**	(R)-**1**	(S)-**1**	(R)-**1**	(S)-**1**	(R)-**1**	(S)-**1**	(R)-**1**
	-30°C		-10°C		0°C		+10°C		+20°C		+30°C	
0:100	-	5.961	-	5.688	-	5.555	-	5.436	-	5.329	-	5.239
5:95	6.707	6.027	6.148	5.726	5.898	5.581	5.678	5.448	5.504	5.337	5.360	5.242
10:90	6.705	6.068	6.156	5.760	5.914	5.612	5.691	5.474	5.518	5.359	5.373	5.261
15:85	6.647	6.118	6.120	5.787	5.885	5.629	5.664	5.480	5.394	5.509	5.352	5.259
25:75	6.571	6.203	6.063	5.831	5.838	5.660	5.640	5.515	5.471	5.378	5.376	5.266
50:50	6.414		5.973		5.768		5.595		5.445		5.319	
60:40	6.326	6.456	5.910	5.988	5.720	5.781	5.545	5.589	5.408	5.443	-[b]	
70:30	6.256	6.529	5.862	6.036	5.683	5.817	5.522	5.621	5.392	5.460	5.280	5.324
80:20	6.200	6.633	5.844	6.121	5.679	5.894	5.520	5.678	5.394	5.509	5.285	5.367
100:0	5.969	-	5.701	-	5.564	-	5.442	-	5.334	-	5.242	-

[a]$CDCl_3$ solution; total concentration 2.35×10^{-2}M.
[b]Not resolved peaks.

Table 3. Non-equivalent ^{1}H NMR chemical shifts of the amide and methyl protons for the mixtures of (S,S)-**4** and (R,R)-**4**[a]

(S,S)-**4**[b] / (R,R)-**4**	δ NH (ppm)								δ CH3 (ppm)							
	(S,S)	(R,R)	(S,S)	(R,R)	(S,S)	(R,R)	(S,S)	(R,R)	(S,S)	(R,R)	(S,S)	(R,R)	(S,S)	(R,R)	(S,S)	(R,R)
	-40°C		-20°C		0°C		20°C		-40°C		-20°C		0°C		20°C	
100:0	6.052	-	5.666	-	5.384	-	5.193	-	1.190	-	1.256	-	1.297	-	1.323	-
80:20	6.081	5.983	5.678	5.621	5.393	5.363	5.202	5.185	1.207	1.281	1.267	1.308	1.303	1.326	1.327	1.338
70:30	6.046	5.990	5.663	5.625	5.389	5.371	5.197		1.224	1.267	1.274	1.300	1.307	1.322	1.330	1.337
60:40	6.053	6.015	5.671	5.648	5.390	5.380	5.199		1.231	1.262	1.277	1.293	1.309	1.322	1.330	1.334
50:50	5.979		5.611		5.355		5.178		1.251		1.292		1.318		1.335	
25:75	5.969	6.057	5.621	5.672	-		-		1.278	1.223	1.307	1.270	1.326	1.309	1.339	1.327
10:90	5.955	6.099	5.600	5.681	5.355	5.394	5.174	5.201	1.297	1.191	1.318	1.260	1.332	1.300	1.343	1.325
5:95	5.925	6.075	5.604	5.689	5.392	5.408	5.172	5.213	1.303	1.193	1.319	1.257	1.334	1.298	1.342	1.323
0:100	-	6.021	-	5.639	-	5.369	-	5.184	-	1.196	-	1.262	-	1.301	-	1.326

[a]$CDCl_3$ solution; total concentration 1.58×10^{-2}M.

Assuming that T_{c2} is the minimum temperature below which the SCADA doublet is non-observable because of high viscosity of the solvent, values $\Delta\delta_{hc}(T)$ at any temperature $T > T_{c2}$ are related to the maximum value $\Delta\delta_{hc}(T_{c2})$ according to the equation:

$$\Delta\delta_{hc}(T) = \Delta\delta_{hc}(T_{c2}) \cdot F[K(T)] \quad (1),$$

where F(K) is a certain function of monomer-associate equilibrium constant K.

Because the phenomena of intermolecular association in solution are too sophisticated to be described in detail, and it was impossible to provide the exact expression of F(K), we have to use some model for approximation to F(K). In such a model of infinite dimension association,[15] after a few assumptions which were made for simplicity (non-cooperative association is restricted by dimerization to describe the data at low concentrations)[15a], we get:

$$F(Kx) = \frac{2Kx+1 - \sqrt{4Kx+1}}{2Kx} \quad (2),$$

where x means the overall enantiomeric content in the solution (x= [S]+[R]).

At certain temperature T_{c1} both free energy of association ΔG_{ass} and F(Kx) are equal to zero, i.e. $\Delta\delta_{hc}(T_{c1}) = 0$. Under real conditions of NMR experiment a signal can be split into a doublet if $F(Kx) \approx 0.05$. Therefore, we assume, according to eq. 1 and 2 and our model,[15c] that the minimal observable value for K equals 5. With this assumption we obtained the data collected in Table 4.

From the values of 1/T and lnK we were able to calculate the thermodynamical parameters:

$$\Delta H = -5.5 \text{ kcal/mol}$$
$$\Delta S = -17 \text{ e.u.}$$

One can also conclude that $\Delta G_{ass}=0$ at +50°C. At +30°C nearly 80% of enantiomers are involved into self-association and at -30°C the participation of self-associated constructs increases to 93%. Such a level of dimerization implies a validity of hypothesis of full dimerization in the sample. If so, fast exchange of enantiomers takes place between the diastereomeric associates. This exchange originates SCAD (Statictically Controlled Associate-Diastereomerism)[3]. If enantiomeric excess is equal zero, i.e. [S]=[R]=x/2, and enantioselectivity in the exchange is absent, then SCAD equilibrium constant equals 1/4.

$$K_{SCAD} = \frac{[SS][RR]}{[SR]^2} = \frac{1}{4}$$

This means that diastereomeric concentrations would be:

$$[SS] = [RR] = 0.125x; \quad [SR] = 0.25x$$

Table 4. The values of parameters calculated according to equations (**1**) and (**2**) at different temperatures.

t°C	-30	-10	0	+10	+20	+30
$10^3/T$	4.115	3.802	3.663	3.533	3.413	3.300
F(Kx)	0.333	0.2228	0.1603	0.1228	0.0965	0.0739
Kx	0.751	0.369	0.217	0.160	0.118	0.086
K	80	39	23	17	12	9
lnK	4.4	3.7	3.14	2.8	2.5	2.2

Experimental section

General

Melting points were determined on a Boetius melting points apparatus and are uncorrected. Solvents and reagents were reaction grade and were used without purification. Tetrahydrofuran (THF) and dioxane were distilled over sodium mirror immediately prior to use. The progress of reaction and the extent of chromatographic purifications were followed by thin-layer chromatography (TLC) on silica-gel plates (Merck). The spots were visualized using a phosphorus-molybdate reagent. Column chromatography was performed using 230-400 mesh silica gel (Merck) and the indicated eluents. ^{1}H(200MHz) and ^{31}P(81MHz) NMR spectra were obtained on a Bruker WP-200 spectrometer for $CDCl_3$ and/or $CHCl_3$ solutions. The chemical shifts are reported in parts per million (ppm) and are positive when downfield from a hexamethyldisiloxane (internal standard) and 85% H_3PO_4 (external standard). Elemental analyses were done by Laboratory of Microanalysis of Nesmeyanov Institute. Optical rotations were measured at 578nm using Polamat A polarimeter, or at 589nm (sodium D line) using Perkin Elmer polarimeter. The aminoalcohols (S)-**2** and (R)-**2** were prepared according to literature precedents.[12,13] Cyclic amidophosphorochloridate (S,S)-**5** and its enantiomer (R,R)-**5** were prepared by the reported procedure.[13] Anilidate (**3**) was prepared by literature method by reacting $POCl_3$ with aniline hydrochloride.[16] 2-Chloro-2-oxo-1,3,2-oxazaphosphorinane (**6**) was prepared according to reported procedure.[17]

The synthesis and separation of (S,S)-4 and (S,R)-4

To a solution of (S)-**2** (8.2g, 46mmol) in anh. dioxane (70mL) were added at rt triethylamine (10.5g, 104mmol) and anilidate **3** (13.0g, 46mmol). The mixture was then allowed to stand at rt for 24h, filtered and the filtrate was concentrated to a sirup residue. Column chromatography (eluent: chloroform-acetone, 4:1) yielded pure (S,S)-**4** (3.2g, 22%) and (S,R)-**4** (2.1g, 14%). Compound (S,S)-**4**: TLC (chloroform-acetone, 4:1) R_f 0.33; mp 166-167°C; ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J=7.0Hz, 3H), 1.64-1.98 (m,2H), 2.72-3.15 (m, 2H), 4.15-4.47 (m, 2H), 4.86 (dq, J=7.0Hz, J=10.3Hz, 1H), 6.30 (d, J=9.0Hz, 1H), 6.87-7.55 (m, 10H); ^{31}P NMR ($CHCl_3$): δ 2.74; $[\alpha]^{25}_D$ -92.3 (c 24.0, MeOH). Anal.Calcd for $C_{17}H_{21}N_2O_2P$: C, 64.55; H, 6.69; N, 8.86. Found: C, 64.73; H, 6.77; N, 8.50. Compound (S,R)-**4**: TLC (chloroform-acetone,

4:1) R_f 0.18; mp 152-153°C; ^{1}H NMR ($CDCl_3$) δ 1.70 (d, J=7.0Hz, 3H), 1.81-2.17 (m, 2H), 2.72-3.41 (m, 2H), 4.23-4.64 (m, 2H), 4.89 (pseudoq, J=8.6Hz, 1H), 6.16 (d, J=8.9Hz, 1H), 6.95-7.35 (m, 10H); ^{31}P NMR ($CHCl_3$) δ 5.49; $[\alpha]^{25}_D$ -16.7 (c, 12.0, MeOH). Anal.Calcd for $C_{17}H_{21}N_2O_2P$: C, 64.55; H, 6.69; N, 8.86. Found: C, 64.32; H, 6.62; N, 8.68.

R-(-)-2-Anilino-2-oxo-1,3,2-oxazaphosphorinane [(R)-1]

Hydrogenolysis of compound (S,S)-**4** (2.5g, 8mmol) in ethanol (50mL) in the presence of 10% Pd/C (0.5g) performed at *ca* 760 mmHg during 5h at 75°C, then for 15h at 65°C, with stirring, afforded a solution which after filtration was evaporated. Column chromatography of the residue (eluent: chloroform-MeOH, 4:1) furnished (R)-**1** (0.87g, 51%) as white crystals: TLC (chloroform-acetone, 1:1) R_f 0.3; mp 190-193°C; ^{1}H NMR ($CDCl_3$) δ 1.72-2.11 (m, 2H), 3.25-3.41 (m, 3H), 4.26-4.45 (m, 2H), 5.32 (d, J=8.4Hz, 1H), 6.90-7.25 (m, 5H); ^{31}P NMR ($CHCl_3$) δ 3.38; $[\alpha]^{25}_D$ -51.0 (c 3.5, MeOH). Anal.Calcd for $C_9H_{13}N_2O_2P$: C, 50.95; H, 6.18; N, 13.20; P, 14.60. Found: C, 51.04; H, 6.05; N, 13.41; P, 14.56.

S-(+)-2-Anilino-2-oxo-1,3,2-oxazaphosphorinane [(S)-1]

Following the procedure used for the preparation of (R)-**1**, the anilidate (R,R)-**4** (1.2g, 3.8mmol) was hydrogenolytically converted to (S)-**1** (0.44g, 53%): TLC (chloroform-acetone, 1:1) R_f 0.3; mp 190-192°C; ^{1}H NMR ($CDCl_3$) δ 1.73-2.16 (m, 2H), 3.22-3.45 (m, 3H), 4.21-4.49 (m, 2H), 5.33 (d, J=8.7Hz, 1H), 7.03-7.25 (m, 5H); ^{31}P NMR ($CHCl_3$) δ 3.38; $[\alpha]^{25}_D$ +50.0 (c 3.5, MeOH). Anal.Calcd for $C_9H_{13}N_2O_2P$: C, 50.95; H, 6.18; N, 13.20; P, 14.60. Found: C, 50.89; H, 6.53; N, 12.84; P, 14.56.

Racemic 2-anilino-2-oxo-1,3,2-oxazaphosphorinane [(R+S)-1]

To a solution of phosphorochloridate **6** (2.0g, 13mmol) and triethylamine (1.52g, 15mmol) in $CHCl_3$ (15mL) was added aniline (1.40g, 15mmol). The solution was stirred at rt for 48hrs and then filtered and evaporated. Column chromatography of the residue (eluent: chloroform-acetone, 1:1) yielded racemic **1** (1.6g, 57%): TLC (chloroform-acetone, 1:1) R_f 0.3; mp 179-181°C (lit.[18] mp. 164°C); ^{1}H NMR ($CDCl_3$) δ 1.72-2.03 (m, 2H), 3.19-3.42 (m, 3H), 4.26-4.52 (m, 2H), 5.34 (d, J=8.3Hz, 1H), 6.91-7.26 (m, 5H); ^{31}P NMR ($CHCl_3$) δ 4.36. Anal.Calcd for $C_9H_{13}N_2O_2P$: C, 50.95; H, 6.18; N, 13.20; P, 14.60. Found: C, 51.06; H, 6.18; N, 13.05; P, 14.45.

(Sc,Sp)-2-Anilino-3-(α-methylbenzyl)-2-oxo-1,3,2-oxazaphosphorinane [(S,S)-4].

To a solution of aniline (0.47g, 5mmol) in anh. THF (15 mL) at -60°C was added butyl lithium (2.4mL of 1.6M solution in hexane) with stirring under nitrogen. After 5 min of stirring at -60°C, a solution of (S,S)-**5** (1.04g, 4 mmol) in THF (5 mL) was added. The mixture was allowed to stirr at -60°C for 10 min, then the cooling bath was removed and stirring was continued for 0.5 hr. The resulting solution was concentrated, chloroform (30mL) was added, and the resulting mixture was washed with 1% HCl(2x20mL), dried over anhydrous Na_2SO_4 and then evaporated to give pale coloured solid (0.7g). Recrystallization (dioxane-pentane) gave white crystals of (S,S)-**4** (0.3g, 27%), TLC (chloroform-acetone, 1:1) R_f 0.50, mp 161-164°C; ^{1}H NMR ($CDCl_3$) 1.33 (d, J=7.0Hz, 3H), 1.61-1.91(m,2H), 2.89-3.16(m,2H), 4.15-4.46(m,2H), 4.97(dq, J=7.0, 10.3Hz, 1H), 5.19(d, J=9.0Hz, 1H), 6.97-7.35(m, 10H); ^{31}P NMR

($CHCl_3$) δ 3.26; $[\alpha]^{25}_{578}$ -117.6 (c 0.97, MeOH). Anal.Calcd for $C_{17}H_{21}N_2O_2P$: C, 64.55; H, 6.69; N, 8.86. Found: C, 64.50; H, 6.98; N, 8.52.

(Rc,Rp)-2-Anilino-3-(α-methylbenzyl)-2-oxo-1,3,2-oxazaphosphorinane [(R,R)-4]

(R,R)-**5** (2.1g, 8 mmol) was dissolved in anh. chloroform (20 mL). Into this solution aniline (0.84g, 9mmol) and triethylamine (0.91g, 9mmol) were added at rt and resulting mixture was then stirred for 30h at rt. The solution was washed with 1% HCl, dried over anhydrous Na_2SO_4 and evaporated to dryness. Recrystallization ($CHCl_3$-hexane) gave white crystals of (R,R)-**4** (1.21g, 48%), TLC (chloroform-acetone, 1:1) R_f 0.50; mp 165-168°C; ^1H NMR ($CDCl_3$) 1.33 (d, J=7.0Hz, 3H), 1.60-1.93 (m, 2H); 2.75-3.18 (m, 2H), 4.14-4.43 (m, 2H), 4.95 (dq, J=7.0, 10.3Hz, 1H), 5.18 (d, J=9.0Hz, 1H), 6.93-7.54 (m, 10H); ^{31}P NMR ($CHCl_3$) δ 3.21; $[\alpha]^{25}_{578}$ +116.2 (c 0.97, MeOH). Anal.Calcd for $C_{17}H_{21}N_2O_2P$: C, 64.55; H, 6.69; N, 8.96. Found: C, 64.55; H, 6.84; N, 8.81.

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