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C−ON Bond Homolysis of Alkoxyamines, Part 11: Activation of the Nitroxyl Fragment

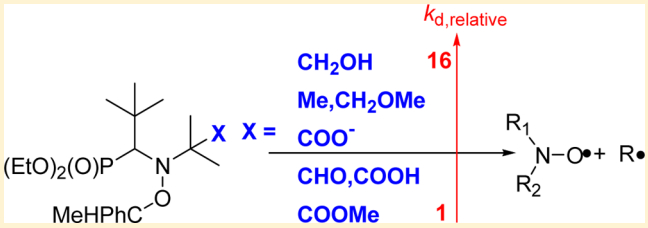
Gérard Audran,*[,†] Paul Brémond,*[,†] Sylvain R. A. Marque,*[,†,‡] and Toshihide Yamasaki[†]

[†]Aix Marseille Université, CNRS, ICR, UMR 7273, 13397 Marseille Cedex 20, France

[‡]N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry SB RAS, Pr. Lavrentjeva 9, 630090 Novosibirsk, Russia

Supporting Information

ABSTRACT: A few years ago, Bagryanskaya and colleagues (*J. Org. Chem.* **2011**) showed that protonation of the nitroxyl fragment deactivated the alkoxyamine C−ON bond. Conversely, our group showed that protonation (*Chem. Commun.* **2011**), as well as other chemical reactions such as oxidation or amine quaternization (*Org. Lett.* **2012**), of the pyridyl moiety carried by the alkyl fragment was suitable to activate the homolysis of the C−ON bond. To pursue our goal of applying alkoxyamines as theranostic agents (*Org. Biomol. Chem.* **2014** and *Mol. Pharmaceutics* **2014**) by activation of the C−ON bond homolysis, we turned our interest to the chemical activation of the nitroxyl fragment by oxidation/reduction of selected functions. Conversion of a hydroxyl group located close to the nitroxyl moiety successively into aldehyde, then acid, and eventually into ester, led to a successive decrease in k_d.



INTRODUCTION

During the last 30 years,[1] tremendous research activity has been devoted to the chemistry of labile alkoxyamines mainly for their application as initiator/controller agents for nitroxide mediated polymerization.[2−8] In 2009, Charles and colleagues[9] proposed that the protonation of the nitroxyl moiety strikingly strengthened the C−ON bond in alkoxyamines. With alkoxyamine **1** as model, Bagryanskaya et al.[10] confirmed that the protonation of the alkyl fragment markedly decreased the homolysis rate constant k_d. Conversely, we showed that protonation,[11] as well as other type of reactions,[12] of the alkyl fragment afforded an increase in k_d. These antagonistic reactivity led to two interesting applications: a new system of coding in materials sciences,[13,14] and new theranostic agents in biology.[15,16] The development of alkoxyamines as theranostic agent requires highly stable alkoxyamines to be transformed into highly labile alkoxyamines, which can be envisioned by activation of either the alkyl fragment or the nitroxyl fragment. Recently, the activation of the pyridyl moiety[12,17] was carefully investigated, as well as that of the alkyl fragment carrying an amine group.[18] Herein, we turned our interest to the deactivation/activation of alkoxyamine models **2**−**5** (Figure 1) via oxidation of suitable functions. The oxidation of the primary hydroxyl function in the vicinity of the nitroxyl moiety into aldehyde and then carboxylic/ester function afforded a clear decrease in k_d (Table 1).

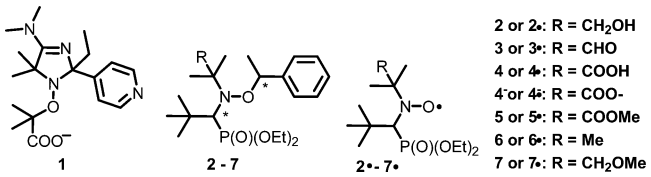


Figure 1. Alkoxyamines discussed in this article.

RESULTS

Preparation of 3−5. Alkoxyamine **2** was oxidized into aldehyde **3** under mild conditions using Dess−Martin periodinane (DMP).[19] The oxidation of **3** into carboxylic acid **4** was performed using Pinnick oxidation procedure.[20] Acid **4** was methylated with methyl iodide to afford ester **5** (Scheme 1).

Recrystallization of (*RR*/*SS*)-**2**,[21,22] (*RR*/*SS*)-**4**[21] and (*RS*/*SR*)-**4**[21] in ethyl acetate/pentane afforded white crystals suitable for X-ray analysis (Figure 2a, c, and d). No intramolecular hydrogen bonding (IHB) is observed in **2** and **4** whereas intermolecular is observed (see SI). Packing in crystal forces to intermolecular H-bonding rather than to IHB in solution (vide infra) and to conformational changes (Figure 2) disfavoring IHB. Indeed, IHB is expected to be favored when C−P bond and C−O bond of hydroxyl group or C−C bond of the carboxylic function are in *syn*-conformation as displayed in Figure 2e,i. The diastereoisomers (*RS*/*SR*)-**2** and (*RR*/*SS*)-**4** are in gauche conformation which requires merely a rotation of 60° to reach the suitable conformation for IHB. On the other hand, diastereoisomer (*RR*/*SS*)-**4** is in a *syn* conformation with the carboxylic function almost eclipsing the *t*-Bu group which requires a rotation of 120° to reach the conformation suitable for IHB. This strongly IHB-disfavoring conformation is due to a combination of the packing forces, intermolecular H-bonding

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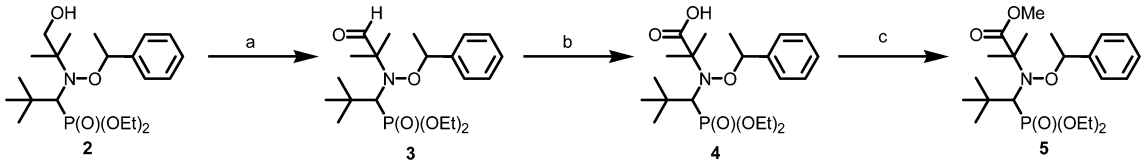
Table 1. Homolysis Rate Constants k_d of 2−7 in Various Conditions (Solvent, Temperature, and pH) and the Subsequent E_a Values As Well As the Re-estimated k'_d Values at 120 °C

			k_d (10^{-4} s^{-1})		E_a (kJ/mol)[b]		k'_d (10^{-3} s^{-1})[c]	
alkoxyamine	solvent[a]	T (°C)	*RS*/*SR*	*RR*/*SS*	*RS*/*SR*	*RR*/*SS*	*RS*/*SR*	*RR*/*SS*
2[d]	*t*-BuPh	90	7.2	5.7	121.8	122.5	15.7	12.7
3	*t*-BuPh	110	9.9	11.2	127.5	127.1	2.7	3.1
4	*t*-BuPh	110	20.9	25.9	125.1	124.5	5.7	7.0
4$^-$	*t*-BuPh + 2 equiv DBU[e]	110	33.1	49.4	123.6	122.3	8.9	13.3
5	*t*-BuPh	100	1.3	1.5	130.6	130.1	1.1	1.2
6[f]	*t*-BuPh	100	4.8	7.6	126.4	125.0	3.8	5.9
7	*t*-BuPh	100	16.0	18.0	122.7	123.2	11.8	10.2
2	H_2O/MeOH (1:1)	80	1.6	0.7	122.8	125.1	11.4	5.7
3	H_2O/MeOH (2:3)	90	0.9	0.7	128.0	128.8	2.4	1.8
4	H_2O/MeOH (3:7) pH = 1.4	90	1.2[g]	1.9[h]	127.2	125.9	3.0	4.5
4$^-$	H_2O/MeOH (1:1) pH = 8.4	100	5.9	8.7	125.8	124.6	4.7	6.7
4$^-$	H_2O/MeOH (1:1) pH = 10.4	90	2.0	2.7	125.6	124.7	4.9	6.4
5	H_2O/MeOH (1:1) pH = 8.4	90	0.4	0.4	130.3	130.5	1.2	1.1
6	H_2O/MeOH (1:1)	80	1.5	1.1	123.0	124.0	10.8	7.9
7	H_2O/MeOH (1:1)	80	1.8	1.2	123.2	123.8	10.7	8.6

[a] *t*-BuPh: *tert*-butylbenzene. [b] Given by eq 3 and using k_d values reported in the 4th and 5th columns. [c] Re-estimated k_d values at 120 °C using eq 3 and E_a values reported in the 6th and 7th columns. [d] E_a = 121.6 kJ/mol for a mixture 70:30 of diastereoisomers, see ref 25. [e] Deprotonation of the carboxylic function was reached using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). [f] E_a = 124.5 kJ/mol for a mixture 1:1 of diastereoisomers, see refs 25 and 24. [g] pK_a = 6.73. [h] pK_a = 7.30.

Scheme 1. Preparation of 3−5[a]



[a] (a) DMP, $NaHCO_3$, CH_2Cl_2. (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH. (c) MeI, K_2CO_3, DMSO.

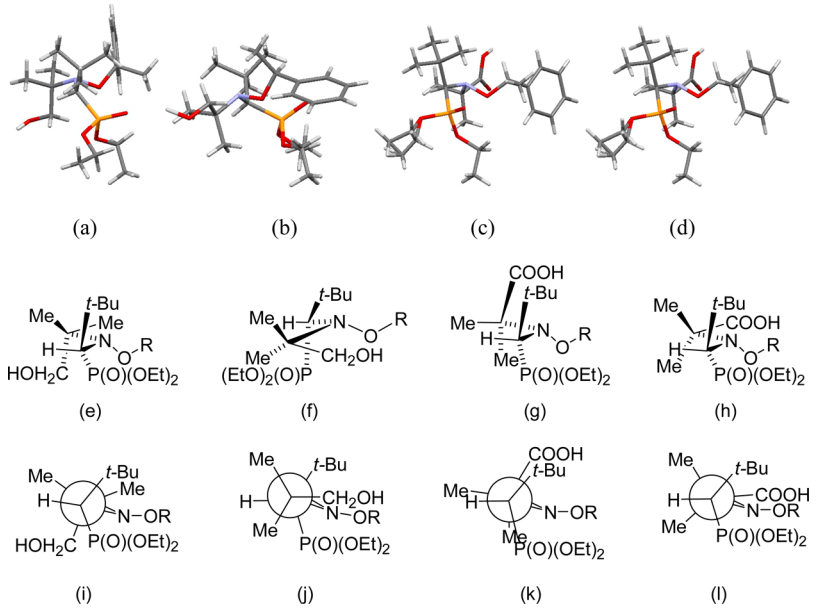


Figure 2. X-ray structures of (a) (*RR*/*SS*)-**2**, (b) (*RS*/*SR*)-**2** (c) (*RR*/*SS*)-**4** and (d) (*RS*/*SR*)-**4** and their subsequent Cram (e−h) and Newman (i−l) projections. Newman projections are performed through the C(P)···C(Me_2) axis. R is for CHMePh group.

and π-stacking between the π sytems of the carboxylic function and the aromatic moiety.

Kinetic Measurements. When the thermolysis of **3** and **5** was investigated by monitoring the growth of the signal of **3**• and **5**• by EPR, no plateau was reached due to a simultaneous decay of **3**• and **5**•, in sharp contrast to **6**•. At this time, no rational can be provided.[23] Furthermore, no EPR signals due to **4**• and **4**$^-$• were detected during the thermolysis of **4** and **4**$^-$.

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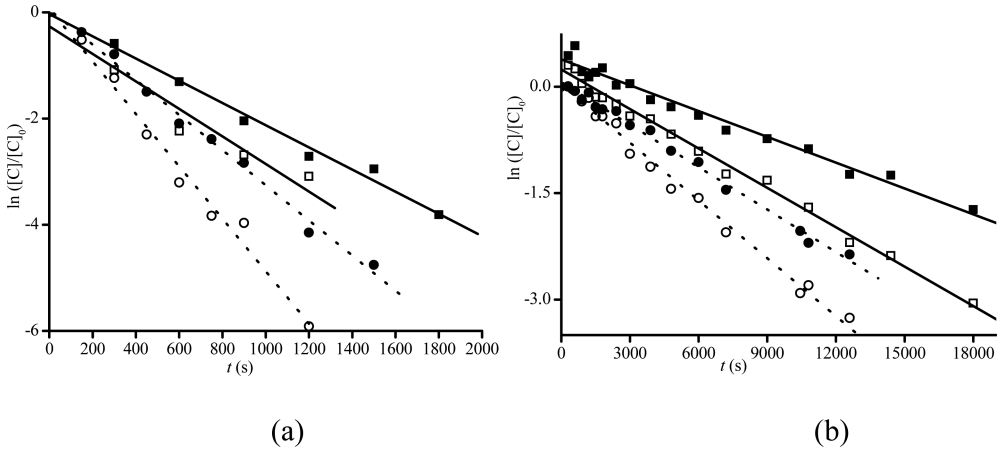

Figure 3. Plot of eq 2 (a) in *t*-BuPh at 110 °C and (b) at T = 90 °C for pH = 1.4 in (H_2O/MeOH: 3/7) and pH = 10.4 (H_2O/MeOH: 1/1). Filled symbols and empty symbols are for the *RS*/*SR* and *RR*/*SS* diastereoisomers, respectively, of **4** (■,□) and **4**$^-$ (●,○).

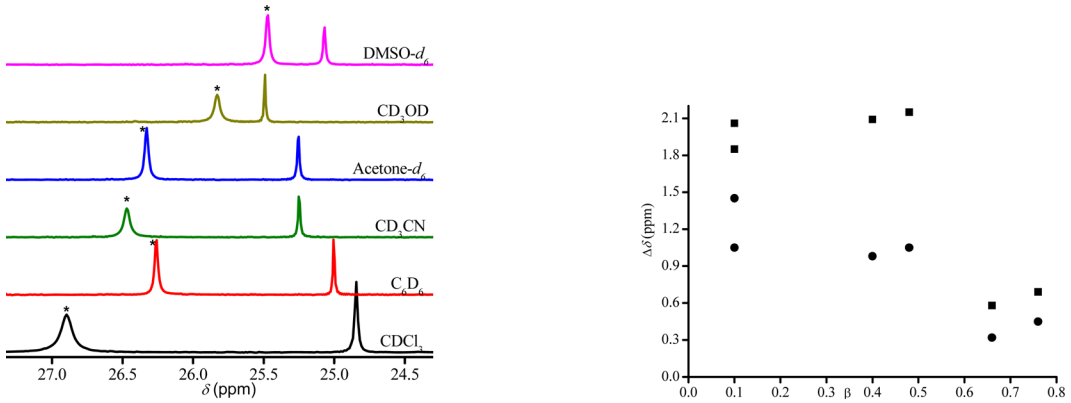

Figure 4. (a) ^{31}P NMR spectra for the *RS*/*SR* diastereoisomers of **2** (left with star) and **7** (right) in the ratio 2:1 (0.03 M) in various solvent. (b) Evolution of the difference Δδ (ppm) between the ^{31}P chemical shifts for **2** and **7** as measured in different solvents versus to the HBA β scale of the corresponding solvents. ■ and ● for *RS*/*SR* and *RR*/*SS* diastereoisomer, respectively.

This low stability of nitroxides **3**•−**5**• led us to investigate the thermolysis of **3**−**5** using ^{31}P NMR.[24] Expected decays were observed both in *tert*-butylbenzene (*t*-BuPh) and in a water/methanol mixture as solvents, as exemplified with the decay of **4** and **4**$^-$ (Figure 3).

$k'_{d,RS/SR}/k'_{d,RR/SS}$ ratii are never larger than 2-fold or smaller than half-fold, as already reported, and do not deserve more comments. The diastereoisomers of **6** were separated and their ratio of 1.55 for k_d is in good agreement with the previously reported data (1.44).[24] The E_a value reported for **2** was for a mixture of diastereoisomers.[24,25] As expected, the difference in k'_d values is negligible (ratio of 1.23).

Intramolecular H-Bonding (IHB). In recent articles, our group highlighted the effect of IHB on k_d values which decreased when IHB occurred between the diethoxyphosphonate group of the nitroxyl fragment and an H-donor group of the alkyl fragment, e.g., OH,[26] COOH,[27] NH_2.[18] On the other hand, the occurrence of IHB in the nitroxide either between the hydroxyl function and the nitroxyl moiety or between the hydroxyl and the diethoxyphosphonate groups as in **2**• was reported to stabilize the nitroxide, and, hence, to increase k_d. However, the occurrence of IHB in **2** was not investigated. The procedure developed to investigate IHB in alkoxyamines carrying a diethoxyphosphonate group[27] was applied to **2** and **4**, using **7** and **5** as respective references, with no IHB and keeping the same polar effect. As displayed in Figure 4a and Table 2, a clear solvent dependence of the difference of chemical shift Δδ between **2** and **7** was observed for both diastereosisomers. In general, the ability of a solvent to suppress

Table 2. ^{31}P NMR Chemical Shifts δ (ppm), Difference in Shift Δδ (ppm) between the *RS*/*SR* and *RR*/*SS* Diastereoisomers of 2 and 7 in Different Solvents at 300 K and the Hydrogen Bond Acceptor Property β of Solvents

	RS/*SR*[a]				*RR*/*SS*[a]		
solvent	δ **2** (ppm)	δ **7** (ppm)	Δδ (ppm)	β[b]	δ **2** (ppm)	δ **7** (ppm)	Δδ (ppm)
$CDCl_3$	26.90	24.84	2.06	0.10	27.08	26.03	1.05
C_6D_6	27.00	25.15	1.85	0.10	27.24	25.82	1.42
MeCN-d_3	27.24	25.15	2.09	0.40	27.33	26.35	0.98
acetone-d_6	26.87	24.72	2.15	0.48	27.22	26.17	1.05
MeOH-d_4	26.14	25.56	0.58	0.66	27.37	27.05	0.32
DMSO-d_6	25.52	24.83	0.69	0.76	26.32	25.87	0.45

[a]85% H_3PO_4 was used as internal reference 0 ppm. Ratio **2**:**7** = 2:1. [b]The values of β are for non deuterated solvents and are given in ref 28.

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IHB is depicted by its ability to accept a hydrogen bond, as given by the hydrogen bond acceptor (HBA) property β.[28] Then, the decrease in $\Delta\delta$ with increasing β values (Figure 4b) from $\Delta\delta$ = 1.05−2.06 in $CDCl_3$ to $\Delta\delta$ = 0.45−0.69 in DMSO-d_6 (Figure 4a and Table 2) implies that the environment of the diethoxyphosphoryl group in **2** and in **7** is clearly different in $CDCl_3$ than in DMSO-d_6. This is a feature of the occurrence of IHB in non HBA solvents such as $CDCl_3$ and benzene as depicted in Figure 5. The diastereosiomers of **2** do not

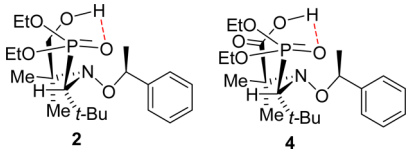

Figure 5. IHB (red dashed bond) in the *RS*/*SR* diastereoisomer of **2** and **4**.

experience the same solvent effect, as highlighted by differences in δ of ca. 0.08−0.35 in $CDCl_3$, benzene-d_6, acetone-d_6 and acetonitrile-d_3, and ca. 1.0 in methanol-d_4 and DMSO-d_6, denoting IHB of different strengths depending on the diastereoisomer although this effect has no significant influence on k_d (Table 1). It must be stressed that k_d depends mainly on the steric hindrance. Then, the occurrence of IHB is expected to change the conformation in each diasteroisomer to different extents which would imply a steric effect antagonist to the IHB, effect affording no difference in k_d.

As in the case of **2**, IHB in **4** was investigated using ^{31}P NMR by comparing $\Delta\delta$ (Figure 6) between **4** and **5** in which IHB did not occur. The decrease in $\Delta\delta$ with increasing β values (Figure 6b) from $\Delta\delta$ = 4.8−5.8 in $CDCl_3$ to $\Delta\delta$ = 0.19−0.23 in DMSO-d_6 (Figure 6 and Table 3) implies that the environment of the diethoxyphosphoryl group in **4** and **5** is clearly different in $CDCl_3$ than in DMSO-d_6, as expected from the occurrence of IHB (Figure 5). As discussed above, the suppression of packing forces, intermolecular H-bonding, and π-staking (Figure 2 and SI) in solution promotes a conformational change to a close conformation suitable for the stabilizing IHB. Nevertheless, there is another effect than the IHB effect which modifies $\Delta\delta$, as highlighted by very similar values of $\Delta\delta$ for $CDCl_3$ and acetonitrile-d_3, as well as for C_6D_6 and acetone-d_6

Table 3. ^{31}P NMR Chemical Shifts δ (ppm), Difference in Shift $\Delta\delta$ (ppm) between the *RS*/*SR* and *RR*/*SS* Diastereoisomers of 4 and 5 in Different Solvents at 300 K and the Hydrogen Bond Acceptor Property β of Solvents

	RS/*SR*[a]				*RR*/*SS*[a]		
solvent	δ **4** (ppm)	δ **5** (ppm)	$\Delta\delta$ (ppm)	β[b]	δ **4** (ppm)	δ **5** (ppm)	$\Delta\delta$ (ppm)
$CDCl_3$	29.82	24.02	5.80	0.10	30.24	25.45	4.80
C_6D_6	27.33	23.78	3.55	0.10	28.46	25.11	3.65
MeCN-d_3	29.65	24.38	5.27	0.40	30.62	25.80	4.82
acetone-d_6	27.42	24.38	3.04	0.48	29.05	25.89	3.15
MeOH-d_4	24.89	24.89	0	0.66	26.50	26.34	0.16
DMSO-d_6	24.00	23.81	0.19	0.76	25.74	25.50	0.23

[a]85% H_3PO_4 was used as the internal reference 0 ppm. Ratio **4**:**5** = 2:1. [b]The values of β are for nondeuterated solvents and are given in ref 28.

despite very different values of β.[29] Interestingly, the diastereoisomers of **4** do not experience the same solvent effect, as highlighted by differences in δ of ca. 0.4 in $CDCl_3$, ca. 0.9−1.1 in acetonitrile-d_3 and benzene-d_6, and ca. 1.6 in other solvents, denoting IHB of different strengths depending on the diastereoisomer, although this effect has no significant influence on k_d (Table 1). The comments made for **2** hold for **4**.

pK_a Determination. pK_a were determined as already reported and are given as 6.73 and 7.30 for *RS*/*SR* and *RR*/*SS* diastereoisomers of **4**, respectively (Figure 7a).[30,31] pK_a were determined from the changes in the chemical shift of the methyl group at position β of the carboxylic function. Other protons were also used and afforded pK_a values differing by less than 0.3.[32] These high values, unusual for carboxylic function, are ascribed to the occurrence of IHB (Figure 5) between the carboxylic function and the diethylphosphoryl group (vide supra). Hence, these high pK_a values might be due either to steric hindrance around the carboxylic function which impedes the approach of the base, to a solvent effect of the mixture MeOH-d_4/D_2O or to a Thorpe−Ingold effect which would change the conformation of the alkoxyamine and would force the occurrence of IHB, affording a lower acidity (i.e., high pK_a values). pK_a of the *RR*/*SS* diastereoisomer is 0.6 unit higher than that of the *RS*/*SR* diastereoisomer. Hence, ^{31}P NMR shift

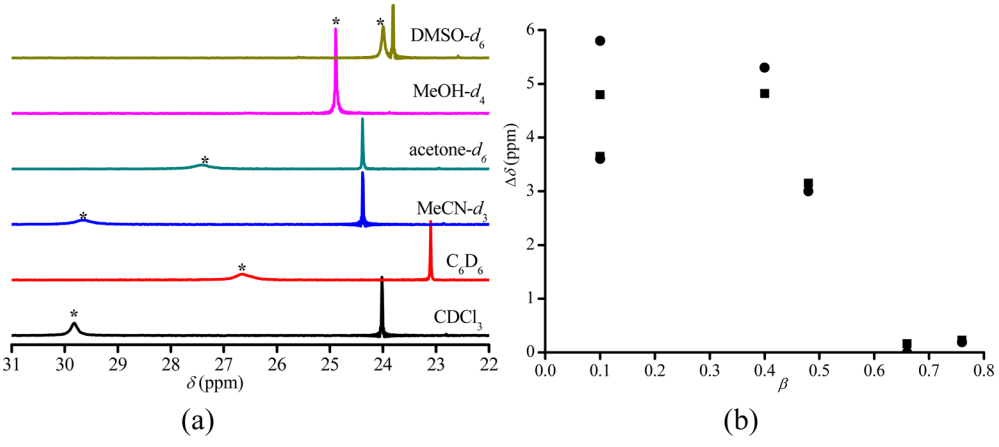

Figure 6. (a) ^{31}P NMR spectra for *RS*/*SR* diastereoisomers of **4** (left with star) and **5** (right) in ratio 2:1 (0.03 M) in various solvents. (b) Evolution of the difference $\Delta\delta$ (ppm) between the ^{31}P chemical shifts for **4** and **5**, as measured in different solvents with respect to the HBA β scale of the corresponding solvents. ■ and ● for *RS*/*SR* and *RR*/*SS* diastereoisomers, respectively.

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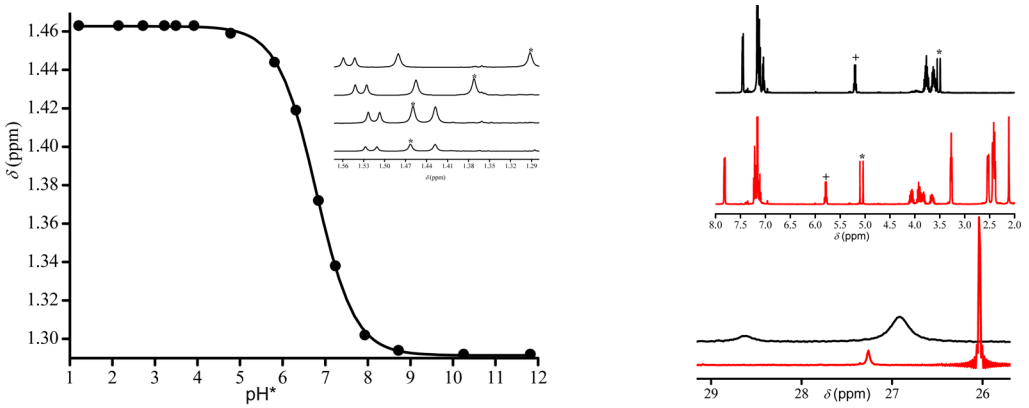

Figure 7. (a) Titration curve for *RS*/*SR* diastereoisomer of **4** (0.01 M in D_2O/MeOH-d_4 1/1). Inset: signal zone of methyl group at the position β to the carboxylic function. Star for the methyl group monitored at pH* of 1.2, 4.8, 6.8, 10.3 from bottom to top. (b) ^{1}H (top) and ^{31}P (bottom) NMR of **4** (top) in C_6D_6 and **4**$^-$ (bottom) in C_6D_6 with 2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Star is for the proton at position β to the nitroxyl moiety and cross for the benzylic proton of the *RS*/*SR* diastereoisomer. ^{31}P NMR was performed with a mixture (2:1) of diastereoisomers *RR*/*SS* and *RS*/*SR*.

δ of the *RR*/*SS* isomer is the larger, denoting a larger partial positive charge on the phosphorus atom for the *RR*/*SS* isomer than for the *RS*/*SR* isomer, the solvent effect on IHB is smaller for the *RR*/*SS* isomer than for the *RS*/*SR* isomer, i.e., $\Delta\Delta\delta$ = 4.64 vs $\Delta\Delta\delta$ = 5.8. The influence of the solvent effect between the diastereoisomers of **4** is larger than that observed for **2**, **5**, and **7**, meaning that IHB in (*RR*/*SS*)-**4** is stronger than in (*RS*/*SR*)-**4** taking into account the higher value of pK_a observed in water/methanol mixture.

The suppression of IHB by adding DBU was checked by ^{1}H and ^{31}P NMR (Figure 7b), and was shown to be total for 2 equiv of DBU.

DISCUSSION

During the last two decades, structure−reactivity relationships have been developed to describe the various effects on k_d of the substituents carried by the alkyl and nitroxyl fragments.[33] It was shown that k_d depend on the stabilization of the released nitroxide, on the polar effect of electron widthdrawing groups (EWG) attached to the nitroxyl moiety, and on the bulkiness of these substituents.[33] Importantly, stabilization and polarity effects are aliased and, then, the various effects are accounted for by eq 1[34] in which the electrical Hammett constant σ_L describes the stabilization/polar effect of EWG, and E_s describes the steric effect of the substituents.[33]

$$\log(k_d/s^{-1}) = -2.98\cdot\sigma_L - 0.86\cdot E_s - 5.83 \quad (1)$$

Thus, it was possible to estimate σ_L of 0.1, 0.28, 0.4, 0.4, 0.59, 0.59, and 0.61 for **4**$^-$, **6**, **7**, **2**−**5**, respectively.[35−37] From eq 1, increasing polarity of EWG leads to a decrease in k_d due to the negative sign of the coefficient. Hence, k_d is expected to decrease in the series **4**$^-$ > **6** > **2** ≈ **7** > **3** ≈ **4** > **5** as σ_L increases. However, **2**, **4** and **7** do not comply with this order (Table 1). Thus, eq 1 was tested with molecules **2**−**5**. Importantly, for molecules such as **2**−**5** belonging to the same family as **6**, the steric effect is not described conventionally due to the leveled steric effect,[38,39] hence, for **2**−**7**, E_s = −5.0. This approach is supported by the very close bulkiness of Me, CH_2OH, COOH (and assuming COO^-), COOR and CHO groups as given by the steric Charton's constant υ.[40,41] As shown in Figure 8,[42] **4**$^-$ like **6** lies on the correlation line, **5** is

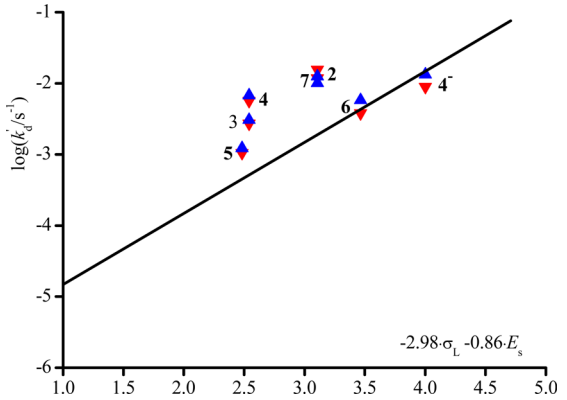

Figure 8. Plot of eq 1 with **2**−**6**. ▲ and ▼ for *RR*/*SS* and *RS*/*SR* diastereoisomer, respectively.

close enough to consider that the effects involved in k_d are described by eq 1 whereas **2**−**4** are clearly outliers. Several years ago, the presence of an intramolecular hydrogen bond was evidenced in **2**• and was expected to stabilize the nitroxide, and hence to increase k_d.[46] It is assumed that the same comment holds for **4**•. Moreover, for **2** and **4**, the occurrence of IHB between the hydroxyl and diethoxyphosphonyl groups is clearly evidenced (vide supra). Although the same bulkiness is assumed for **2**−**6**, an increase in the steric hindrance in **2** and **4** due to the occurrence of IHB cannot be discarded. For some cases, the steric leveled effect does not hold.[43] In general, the minimal steric interaction principle[40] is obeyed affording the conformation exhibiting the lower steric hindrance except that for **7**, as most bond rotations are suppressed in the nitroxyl fragment,[44,45] the bulkiness of the CH_2OMe group[41] plays its role. The latter is not accounted for by the model used to describe E_s,[33] affording an upward deviating data. E_a of **7** is very close to E_a of **2** (1 kJ/mol of difference) and ca. 5 kJ/mol lower than the expected value given by eq 1 ($k'_d = 2 \times 10^{-3}$ s^{-1} and E_a = 128.5 kJ/mol) meaning that the steric effect, i.e., the increase in bulkiness due to the size of the CH_2OMe group,[41] matches the effect of IHB observed in **2**. The case of **3** is more puzzling and at this time no rational can be provided.

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The C−ON bond homolysis in **2**−**6** was also investigated in water/methanol mixtures. However, the discussion is less obvious than for the experiments performed in *t*-BuPh because some of the values of σ_L might be dependent on the solvent, and some unexpected solvation effect might occur both for the reactants and the products. Nevertheless, k_d decreases in the series **2** > **6** ≈ 7 > **4**$^-$ > **4** ≥ **3** > **5** for the *RR*/*SS* diasteroisomer and in the series **6** ≈ **2** ≈ 7 > **4**$^-$ > **4** ≈ **3** > **5** for the *RS*/*SR* diastereoisomer whereas, from eq 1, one would expect **4**$^-$ ≥ **6** > **2** ≈ 7 > **3** ≈ **4** > **5**. Thus, the general trend is the expected one, with some discrepancy such as a weak effect of the anion form of **4** which might be due to a better solvation of **4**$^-$ than **4**.

CONCLUSION

The oxidation of CH_2OH into COOMe afforded a clear decrease in k_d, as expected from eq 1. This shows that increasing the polarity of the substituent implies a decrease in k_d. The virtual reduction of the ester group into hydroxyl is expected to increase k_d. Thus, we successfully proposed a new mode of activation/deactivation of alkoxyamines based on the oxidation/reduction of a suitable function in the vicinity of the nitroxyl moiety. Indeed, in the aim to apply these alkoxyamines as theranostic agents,[15] the hydrolysis of the peptide ester group of analogue of **5** by enzymes into its carboxylate salt would afford a ca. 10-fold decrease of the half-life time $t_{1/2}$ at 37 °C in water/methanol, e.g., for (*RR*/*SS*)-**5** $t_{1/2}$ = 302 days and for (*RR*/*SS*)-**4**$^-$ $t_{1/2}$ = 33 days

EXPERIMENTAL SECTION

Alkoxyamines **2** and **6** were prepared as previously reported.[46] Since nitroxides **3**•−**5**•, released during the thermolysis of alkoxyamines **3**−**5**, were not stable enough to be monitored by Electron Paramagnetic Resonance (EPR), k_d were determined, using ^{31}P NMR as previously described using TEMPO as alkyl radical scavenger.[24] k_d for **2**, **6** and **7** were determined by EPR. The alkoxyamine decay was monitored to completion. k_d were given by eq 2. Activation energies E_a were estimated using eq 3 and the averaged frequency factor $A = 2.4 \times 10^{14}$ s^{-1}.[25,33] The values of k_d and E_a are listed in Table 1.

$$\ln \frac{[\text{alkoxyamine}]_t}{[\text{alkoxyamine}]_0} = -k_d \cdot t \quad (2)$$

$$E_a = 8.314 \cdot T \cdot \ln \frac{2.4 \cdot 10^{14}}{k_d} \quad (3)$$

General Experimental Methods. All solvents were used as received. Routine reaction monitoring was performed using silica gel 60 F_{254} TLC plates; the spots on plates were visualized, first under UV light and then by heating the plates stained with a phosphomolybdic acid solution in EtOH. Purification by column chromatography was performed on silica gel 60 (230−400 mesh). ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ on a 300 or a 400 MHz spectrometer. Chemical shifts (δ) in ppm are reported using residual nondeuterated solvents as internal reference for ^{1}H and ^{13}C NMR spectra, and 85% H_3PO_4 for ^{31}P NMR spectra.

*Diethyl (2,2-dimethyl-1-((1,1-dimethyloxoethyl)(1-phenylethoxy)amino)propyl) phosphonate (RS/SR-**3**).* To a stirred solution of (*RS*/*SR*)-**2** (0.82 g, 2.0 mmol) and $NaHCO_3$ (0.83 g, 9.9 mmol) in CH_2Cl_2 (30 mL) was added Dess−Martin periodinane (DMP) (1.25 g, 3.0 mmol) at 0 °C. The mixture was stirred for 5 h at 0 °C, then quenched with Na_2SO_3 (50 mL, 10%) and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography eluting with CH_2Cl_2 to afford *RS*/*SR*-**3** (0.58 g, 72%). White crystals; mp 81−83 °C; R_f = 0.54 (Pentane:EtOAc = 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J_{H-H} = 7.1 Hz, 3H); 1.23 (s, 15H), 1.27 (t, J_{H-H} = 9.71 Hz, 3H), 1.58 (d, J_{H-H} = 6.5 Hz, 3H), 3.41 (d, J_{H-P} = 25.8 Hz, 1H), 3.17−3.50 and 3.82−4.03 (m, 4H), 5.27 (q, J_{H-H} = 6.5 Hz, 1H), 7.20−7.36 (m, 5H), 9.74 (s, 1H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 75 MHz) δ 15.9 (d, J_{C-P} = 6.6 Hz), 16.1 (d, J_{C-P} = 6.1 Hz), 18.2 (s), 21.4 (s), 22.4 (s), 30.1 (d, J_{C-P} = 6.1 Hz), 35.1 (d, J_{C-P} = 5.0 Hz), 59.0 (d, J_{C-P} = 7.2 Hz), 61.7 (d, J_{C-P} = 6.6 Hz), 69.3 (d, J_{C-P} = 141.4 Hz), 70.9 (s), 78.9 (s), 127.4 (s), 127.5 (s), 127.8 (s), 142.0 (s), 201.9 (s); ^{31}P{^{1}H}-NMR ($CDCl_3$, 162 MHz) δ ppm 23.14; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{21}H_{37}NO_5P$ 414.2404, found 414.2403.

*Diethyl (2,2-dimethyl-1-((1,1-dimethyloxoethyl)(1-phenylethoxy)amino)propyl) phosphonate (RR/SS-**3**).* Compound (*RR*/*SS*)-**3** was synthesized by the same procedure as for compound *RS*/*SR*-**3**. (*RR*/*SS*)-**2** (0.16 g, 0.38 mmol), $NaHCO_3$ (0.16 g, 1.89 mmol) and DMP (0.24 g, 0.57 mmol) afforded (*RR*/*SS*)-**3** (0.14 g, 88%) as white crystals; mp 63−66 °C; R_f = 0.42 (Pentane:EtOAc = 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 3H), 1.17 (s, 3H), 1.28 (s, 9H), 1.34 (t, J_{H-H} = 7.0 Hz, 3H); 1.37 (t, J_{H-H} = 7.0 Hz, 3H), 1.55 (d, J_{H-H} = 6.7 Hz, 3H), 3.36 (d, J_{H-P} = 25.8 Hz, 1H), 3.96−4.42 (m, 4H), 5.10 (q, J_{H-H} = 6.6 Hz, 1H), 7.24−7.37 (m, 5H), 8.91 (s, 1H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 75 MHz) δ 16.1 (d, J_{C-P} = 7.2 Hz), 16.5 (d, J_{C-P} = 5.5 Hz), 18.1 (s), 23.1 (s), 29.7 (d, J_{C-P} = 5.5 Hz), 35.4 (d, J_{C-P} = 5.5 Hz), 59.3 (d, J_{C-P} = 7.2 Hz), 61.7 (d, J_{C-P} = 6.6 Hz), 68.8 (d, J_{C-P} = 140.3 Hz), 71.2 (s), 84.0 (s), 127.1 (s), 127.8 (s), 128.2 (s), 143.6 (s), 202.2 (s); ^{31}P{^{1}H}-NMR ($CDCl_3$, 162 MHz) δ ppm 24.38. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{21}H_{37}NO_5P$ 414.2404, found 414.2403.

*2-((1-(Diethoxyphosphoryl)-2,2-dimethylpropyl)(1-phenylethoxy)amino)-2-methyl propanoic acid (RS/SR-**4**).* To a solution of (*RS*/*SR*)-**3** (0.38 g, 0.92 mmol) in ^{t}BuOH (5 mL) and 2-methyl-2-butene (0.98 mL, 9.26 mmol) was added a mixed solution of $NaClO_2$ (0.17 g, 1.8 mmol) in 6% NaH_2PO_4 (4 mL) in water at rt. The mixture was stirred overnight, and then diluted with water, acidified with 1 M HCl and extracted with CH_2Cl_2. The combined organic phase was dried with $MgSO_4$ and the solvent was evaporated in vacuo. The crude residue was purified by flash column chromatography (CH_2Cl_2: acetone = 97:3) to afford (*RS*/*SR*)-**4** (0.29 g, 73%). white crystals; mp 121−123 °C (decomp.); R_f = 0.25 (CH_2Cl_2: acetone = 9:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.03−1.18 (m, 12 H), 1.28 (t, J_{H-H} = 6.5 Hz, 3 H), 1.50 (s, 3 H), 1.55 (d, J_{H-H} = 6.1 Hz, 3 H), 1.56 (s, 3 H), 3.43 (d, J_{H-P} = 24.5 Hz, 1 H), 3.65−4.18 (m, 4 H), 4.99 (q, J_{H-H} = 6.3 Hz, 1 H), 7.18−7.39 (m, 5 H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 75 MHz) δ ppm 15.8 (d, J_{C-P} = 6.6 Hz), 16.0 (d, J_{C-P} = 5.5 Hz), 21.5 (s), 24.5 (s), 25.2 (br. s.), 29.8 (d, J_{C-P} = 6.1 Hz), 34.9 (d, J_{C-P} = 5.0 Hz), 60.0 (d, J_{C-P} = 7.2 Hz), 62.1 (d, J_{C-P} = 6.6 Hz), 69.2 (d, J_{C-P} = 139.8 Hz), 68.7 (s), 79.7 (s), 127.2 (s), 127.7 (s), 142.4 (s), 176.4 (s); ^{31}P{^{1}H}-NMR ($CDCl_3$, 162 MHz) δ ppm 29.83; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{21}H_{37}NO_6P$ 430.2353, found 430.2351.

*2-((1-(Diethoxyphosphoryl)-2,2-dimethylpropyl)((1-phenylethoxy)amino)-2-methyl propanoic acid (RR/SS-**4**).* (*RR*/*SS*)-**4** was synthesized following same procedure as for (*RS*/*SR*)-**4**. (*RR*/*SS*)-**3** (0.15 g, 0.37 mmol), 2-methyl-2-butene (0.40 mL, 3.73 mmol) and $NaClO_2$ (0.13 g, 1.44 mmol) afforded (*RR*/*SS*)-**4** (0.12 g, 72%) as white crystals; mp 131−133 °C. R_f = 0.26 (CH_2Cl_2: acetone = 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.13 (s, 9 H), 1.18 (t, J_{H-H} = 7.1 Hz, 3 H), 1.24 (br. s., 3 H), 1.27 (t, J_{H-H} = 7.0 Hz, 3 H), 1.37 (s, 3 H), 1.50 (d, J_{H-H} = 6.6 Hz, 3 H), 3.33 (d, J_{H-P} = 24.5 Hz, 1 H), 3.73−4.21 (m, 4 H), 4.98 (q, J_{H-H} = 6.6 Hz, 1 H), 7.16−7.32 (m, 5 H). ^{13}C{^{1}H}-NMR ($CDCl_3$, 75 MHz) δ ppm 16.1 (d, J_{C-P} = 6.6 Hz), 16.4 (d, J_{C-P} = 5.5 Hz), 22.3 (s), 25.5 (br. s.), 29.5 (d, J_{C-P} = 5.5 Hz), 35.3 (d, J_{C-P} = 6.6 Hz), 61.3 (d, J_{C-P} = 7.2 Hz), 62.1 (d, J_{C-P} = 7.2 Hz), 68.7 (d, J_{C-P} = 146.4 Hz), 69.8 (s), 83.0 (s), 127.2 (s), 127.6 (s), 128.0 (s), 142.5 (s), 176.2 (s); ^{31}P{^{1}H}-NMR ($CDCl_3$, 162 MHz) δ ppm 30.29. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{21}H_{37}NO_6P$ 430.2353, found 430.2351.

*Methyl 2-((1-(diethoxyphosphoryl)-2,2-dimethylpropyl)(1-phenylethoxy)amino)-2-methylpropanoate (RS/SR-**5**).* To a mixed solution of (*RS*/*SR*)-**4** (0.25 g, 0.6 mmol) and K_2CO_3 (0.81 g, 5.9 mmol) was added MeI (0.04 mL, 0.7 mmol) in DMSO at rt. After stirring during 1 h, H_2O was added and the mixture was extracted with

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Et_2O. The combined organic phase was dried with $MgSO_4$ and the solvent was evaporated. The crude was purified by flash column chromatography (CH_2Cl_2:acetone = 98:2) to afford (*RS*/*SR*)-**5** (0.25 g, 97%). white crystal; mp 57−59 °C; R_f = 0.54 (CH_2Cl_2: acetone =9:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.89 (t, J_{H-H} = 7.1 Hz, 3 H), 1.21 (s, 9 H), 1.24 (t, J_{H-H} = 7.1 Hz, 3 H), 1.41 (s, 3 H), 1.53 (d, J_{H-H} = 6.0 Hz, 3 H), 1.54 (s, 3 H), 3.12−3.40 (m, 2 H), 3.68 (s, 3 H), 3.77−4.02 (m, 2 H), 3.84 (d, J_{H-P} = 26.5 Hz, 1 H), 5.25 (q, J_{H-H} = 6.6 Hz, 1 H), 7.19−7.32 (m, 3 H), 7.41−7.49 (m, 2 H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 75 MHz) δ ppm 16.0 (d, J_{C-P} = 6.6 Hz), 16.2 (d, J_{C-P} = 5.0 Hz), 20.8 (s), 25.0 (s), 25.6 (s), 30.0 (d, J_{C-P} = 6.1 Hz), 34.9 (d, J_{C-P} = 5.0 Hz), 51.4 (s), 58.4 (d, J_{C-P} = 7.7 Hz), 62.0 (d, J_{C-P} = 6.1 Hz), 67.5 (s), 69.7 (d, J_{C-P} = 142.0 Hz), 78.8 (s), 127.4 (s), 127.7 (s), 127.8 (s), 142.4 (s), 173.2 (s); ^{31}P{^{1}H}-NMR ($CDCl_3$, 162 MHz) δ ppm 24.03; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{22}H_{39}NO_6P$ 444.2510, found 444.2509.

Methyl 2-((1-(diethoxyphosphoryl)-2,2-dimethylpropyl)(1-phenylethoxy)amino)-2-methylpropanoate (RR/SS-5). (*RR*/*SS*)-**5** was synthesized by the same procedure as (*RS*/*SR*)-**5**. (*RR*/*SS*)-**4** (47 mg, 0.11 mmol), K_2CO_3 (76 mg, 0.55 mmol) and MeI (8.3 μL, 0.13 mmol) afforded (*RR*/*SS*)-**5** (43 mg, 89%) as white crystals; mp 67−69 °C; R_f = 0.37 (CH_2Cl_2:acetone = 9:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.94 (s, 3 H), 1.25 (s, 3 H), 1.27 (s, 9 H), 1.35 (t, J_{H-H} = 7.1 Hz, 3 H), 1.32 (t, J_{H-H} = 7.1 Hz, 3 H), 1.56 (d, J_{H-H} = 6.8 Hz, 3 H), 3.38 (s, 3 H), 3.67 (d, J_{H-P} = 25.8 Hz, 1 H), 3.90−4.43 (m, 4 H), 5.09 (q, J_{H-H} = 6.7 Hz, 1 H), 7.27 (s, 5 H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 75 MHz) δ ppm 16.2 (d, J_{C-P} = 6.6 Hz), 16.7 (d, J_{C-P} = 4.4 Hz), 24.3 (s), 24.6 (s), 26.9 (s), 29.6 (d, J_{C-P} = 6.1 Hz), 35.5 (d, J_{C-P} = 6.1 Hz), 51.5 (s), 58.8 (d, J_{C-P} = 7.2 Hz), 62.1 (d, J_{C-P} = 6.1 Hz), 67.6 (s), 69.5 (d, J_{C-P} = 140.3 Hz), 85.7 (s), 126.5 (s), 126.9 (s), 128.0 (s), 145.1 (s), 173.8 (s); ^{31}P{^{1}H}-NMR ($CDCl_3$, 162 MHz) δ ppm 25.45. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{22}H_{39}NO_6P$ 444.2510, found 444.2509.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02790.

Characterization data (^{1}H, ^{13}C, ^{31}P NMR spectra) of compounds **2**−**5**, procedure for kinetic and pK_a measurements and for intramolecular H-bonding. (PDF)

X-ray crystallographic data of (*RR*/*SS*)-**2**. (CIF)

X-ray crystallographic data of (*RS*/*SR*)-**2**. (CIF)

X-ray crystallographic data of (*RR*/*SS*)-**4**. (CIF)

X-ray crystallographic data of (*RS*/*SR*)-**4**. (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: g.audran@univ-amu.fr.

*E-mail: paul.bremond@univ-amu.fr.

*E-mail: sylvain.marque@univ-amu.fr.

Notes

The authors declare no competing financial interest.

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