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Deuterium-Labeling and NMR Study of the Dearomatization of *N*-Alkyl-*N*-benzyldiphenylphosphinamides through Anionic Cyclization: Ortho and Benzylic Lithiation Directed by Complex-Induced Proximity Effects

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Abstract: The mechanism of the anionic cyclization dearomatizing reaction of *N*-benzyl-*N*-methyldiphenylphosphinamide (**1**) upon treatment with *s*-BuLi in tetrahydrofuran (THF) at −90 °C has been analyzed by deuterium-labeling and natural abundance multinuclear magnetic resonance (^{1}H, ^{2}H, ^{7}Li, ^{13}C, ^{31}P) studies. In the absence of coordinating cosolvents such as hexamethylphosphoramide (HMPA), eight major anionic species were identified, which allowed us to unravel the pathway of the metalation reaction. In agreement with the complex-induced proximity effect (CIPE) mechanism, the sequence of transformations emerging from this study involves the coordination of the lithium base to the P═O group of **1** to give four dimeric precomplexes whose NMR data are consistent with structures **Va/Vb** and **VIIIa/VIIIb**. The diastereomers **Va/Vb** are the precursors of the monomeric benzylic anion **II**, whereas the **VIIIa/VIIIb** diastereomers are assumed to undergo ortho deprotonation leading to anions **I**. Translocation from the ortho anion to the benzylic one is not observed. Intramolecular conjugate addition of anion **II** to the *P*-phenyl rings happens in a reversible way, affording the monomeric dearomatized anions **III**, **IV**, **VI**, and **VII**. The reaction progresses to yield a mixture containing only the species **I**, **III**, and **IV**. HMPA acts as a catalyst for the ortho-to-benzylic translocation and anionic cyclization reactions. Two-dimensional (2D) ^{7}Li,^{31}P{^{1}H} shift correlations and ^{7}Li{^{31}P} NMR spectra proved to be crucial for the structural assignment of the anionic species. These techniques also demonstrated the diastereotopicity of the two achiral ligands involved in a dimer with *s*-BuLi (**Vb**) owing to the slow configuration inversion of the carbanion center.

Introduction

Dearomatization reactions of aromatic hydrocarbons have attracted much attention for quite some time. This continued interest is driven by the possibility of using low-cost and readily accessible starting materials for the construction of functionalized carbocyclic compounds with a defined substitution pattern and stereochemistry in a one-pot process.[1] The intermolecular conjugate addition of a nucleophile to an electron-deficient aromatic hydrocarbon is one of the methods best suited to breaking down the conjugated π system of an aromatic ring.[2] The usefulness of this strategy has been demonstrated through the preparation of a series of natural bioactive substances[3] and some biomimetics.[4] The initial dearomatized products have also been further manipulated to provide heterocyclic derivatives.[5] A more efficient alternative to this approach is provided by the anionic cyclization dearomatizing methodology.[6] The general procedure consists of the formation of a carbanion adjacent to a heteroatom through a metalation reaction directed by an electron-withdrawing group, which also activates the aromatic ring toward the subsequent intramolecular nucleophilic attack. Amides,[7] sulfones,[8] sulfonamides,[9] and phosphinamides[10] are suitable functional groups for this dual role and have enabled the introduction of nitrogen, sulfur, and phosphorus heteroatoms, respectively, into the heterocyclic moiety of dearomatized systems. The dearomatized compounds have been used as

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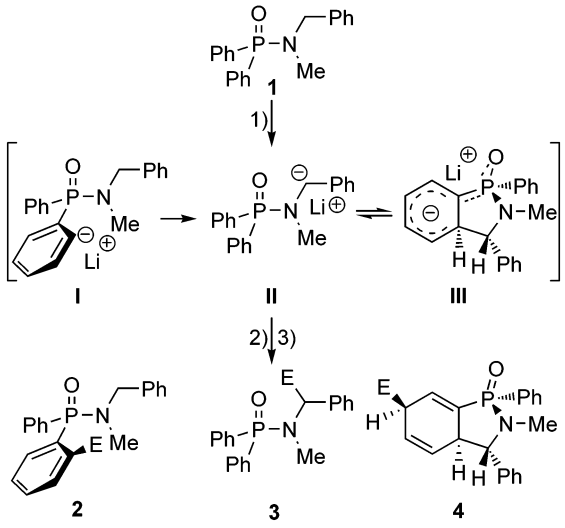
building blocks for the synthesis of kainoids,[11] natural products analogues,[8c,12] and functionalized γ-aminophosphinic acids.[10,13] Recently, Clayden et al. demonstrated the feasibility of using two different groups for aromatic ring activation and anion stabilization in the dearomatization of oxazolylnaphthalenes bearing an ether appendage.[6,14] Upon metalation in the α position with respect to the oxygen atom, the oxazoline Michael acceptor[15] drives an anionic cyclization reaction, yielding dearomatized oxygen heterocycles.[16]

The optimization of the dearomatization−electrophilic trapping reactions of *N*-alkyl-*N*-benzyl(diphenyl)phosphinamides revealed some mechanistic hints that can be summarized as follows:[17] (1) coordinating solvents such as hexamethylphosphoramide (HMPA) or 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) notably accelerate the reaction, the best results being obtained with the latter; (2) significant amounts of products derived from ortho and benzylic metalation were formed for short metalation (t_1) and electrophilic quenching (t_2) times; and (3) the anionic cyclization step is reversible, which allows one to obtain products of either kinetic or thermodynamic control. The general picture emerging from these experimental results is shown in Scheme 1 for the particular case of *N*-benzyl-*N*-methyl(diphenyl)phosphinamide (**1**). The products isolated (**2**, **3**, and **4**) are consistent with the participation of three possible anions: the ortho-lithiated species **I**, the benzylic derivative **II**, and the dearomatized intermediate **III**. This situation is similar to that reported for the anionic cyclization of *N*-benzylarylamides.[18] By analogy with the mechanism proposed for the dearomatization of these compounds, we assumed that the ortho anion may translocate to the benzylic one. It must be pointed out that Clayden et al. suggested that the cyclization step of

Scheme 1[a]



[a] (1) *s*-BuLi (2.5 equiv), DMPU (none or 6 equiv), THF, −90 °C, t_1. (2) E^+, −90 °C, t_2. (3) H_2O.

lithiated arylamides is better described as an electrocyclic ring closure rather than a standard Michael addition.[19]

The reactions that produce anions **I** and **II** upon treatment of phosphinamide **1** with *s*-BuLi are examples of ortho- and benzylic-directed metalation, respectively. Directed lithiations are a topic of considerable debate.[20] The selective deprotonation of an ortho or benzylic position assisted by an electron-withdrawing group bearing electron lone pairs may be explained through the complex-induced proximity effect (CIPE) model.[21] This mechanism considers the lithiation as a two-step process. First, the coordination of the lithium cation of the base with one Lewis basic heteroatom of the substrate results in the formation of a complex. This complex brings the carbanionic center of the base close to the acidic proton, thus favoring the transfer of the proton in the second step. Ortho-directed deprotonations have been interpreted by an alternative mechanism involving a one-step reaction. In this model, the metalation is described as a kinetically controlled transformation for which the term "kinetically enhanced metalation" has been coined.[22] A detailed analysis of the lithiation of phosphinamides in THF solution in terms of these models has not been previously performed. In this article we describe the isotopic-labeling and NMR study of the mechanism of the reaction of *N*-alkyl-*N*-benzyl(diphenyl)phosphinamides with *s*-BuLi leading to dearomatized products. Deuteration reactions afforded the distribution of anionic species present in the reaction medium, and the use of deuterated phosphinamides showed the feasibility of anion translocation. NMR monitoring of the reaction made possible identification of all the intervening lithiated intermediates and

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demonstrated the existence of an equilibrium between the dearomatized anions corresponding to the kinetic and thermodynamic products of the reaction. The study also showed that deprotonation of **1** is preceded by a precomplexation step in which the base and the phosphinamide are held in close proximity. ^{7}Li,^{31}P shift correlations were used to establish the connectivity between the ^{7}Li,^{31}P spin pairs of each species. The role of coordinating cosolvents has been elucidated by performing the NMR measurements both in the presence and absence of HMPA.

Results and Discussion

First, we will comment on the results obtained from deuteration reactions of dearomatized **1** and dearomatization of deuterium-labeled phosphinamides. Second, an extensive NMR study of the lithiation of **1** will be discussed. Within each section the experiments performed in the absence of cosolvent are treated first, and the effects of the addition of HMPA are analyzed subsequently.

Isotopic-Labeling Studies. The general reaction conditions for the synthesis of the benzoazaphospholes **4** (Scheme 1) consisted of the treatment of a THF solution of **1** and 6 equiv of DMPU (or HMPA) with 2.5 equiv of *s*-BuLi at −90 °C for t_1 min, followed by the addition of the appropriate electrophile and stirring for t_2 min at the same temperature. Unless otherwise stated, the starting phosphinamide used throughout the text will be **1**. Phosphinamide **1** contains only one benzylic moiety, and in terms of NMR, the methyl group is a good reporter of the transformations that **1** may experience along the reaction pathway. The reaction times t_1 and t_2 were optimized for each electrophile; $t_1 = t_2 = 30$ min for trapping the dearomatized species with organic protonating agents,[13] whereas for aldehydes the process was completed for reaction times as short as $t_1 = t_2 = 1$ min.[17] These differences mirror the different reaction rates of the lithiated species present in the medium toward a proton or a carbonyl group. The proton is so reactive that it irreversibly quenches all anions immediately and in an indiscriminate manner. The fact that in the sequence of dearomatization−protonation reactions the metalation step requires 30 min to achieve good yields of dearomatized products indicates that this time is necessary for the evolution of the ortho and benzylic anions to the dearomatized lithiated species. Otherwise, protonation of these two types of anions will regenerate the starting phosphinamide.[23] In sharp contrast, aldehydes react very rapidly and selectively with the dearomatized nucleophile, driving the equilibrium among the anions to the dearomatized species, which is consumed through reaction with the aldehyde.

To determine the anion distribution at a given metalation time, we used D_2O as quench reagent (Scheme 1). Assuming an almost negligible isotopic effect of D_2O versus H_2O, deuteration of the anions **I** to **III** will provide three different products: **2-*d***, **3-*d*,** and **4-*d*** (in all cases E = ^{2}H without the equilibration observed when the electrophile was an aldehyde). Thus, a series of experiments was performed in which phosphinamide **1** was lithiated as stated above for a time t_1. No cosolvent was used because in the presence of DMPU or HMPA the anionic cyclization is too rapid to establish any reasonable trend between the anions.[17] The reactions were quenched with D_2O/THF at −90 °C for 30 min, and then aqueous workup gave the crude mixtures that were analyzed through their ^{1}H, ^{2}H, and ^{31}P NMR spectra. As a result of the very small chemical shift difference between **2-*d*** and **3-*d***, the ^{1}H and ^{31}P NMR spectra afforded only the ratio of dearomatized versus open-chain products obtained. In contrast, ^{2}H NMR spectra allowed us to readily identify all deuterated compounds because each deuterium absorbed in a well-separated region of the spectrum. Figure 1 shows the measured ^{2}H NMR spectra, and Table 1 gives the distribution of products as a function of t_1 deduced from the integrals of the respective product signals in the spectra. Previous studies[10a,13] have shown that quenching the dearomatized anions with H_2O and MeOH affords mixtures of products arising from the protonation at the alpha (cis/trans isomers at the bridging carbon atoms), gamma, and epsilon positions with respect to the phosphorus atom. To prevent confusion, we grouped all deuterated dearomatized compounds under the generic label **4-*d***. The deuterium signal corresponding to the epsilon derivative is clearly seen in all spectra at $\delta = 2.2$ ppm (relative yield of 3%). In the spectrum measured at $t_1 = 12$ h, the ^{2}H signals of the products having a deuterium atom at the alpha and gamma

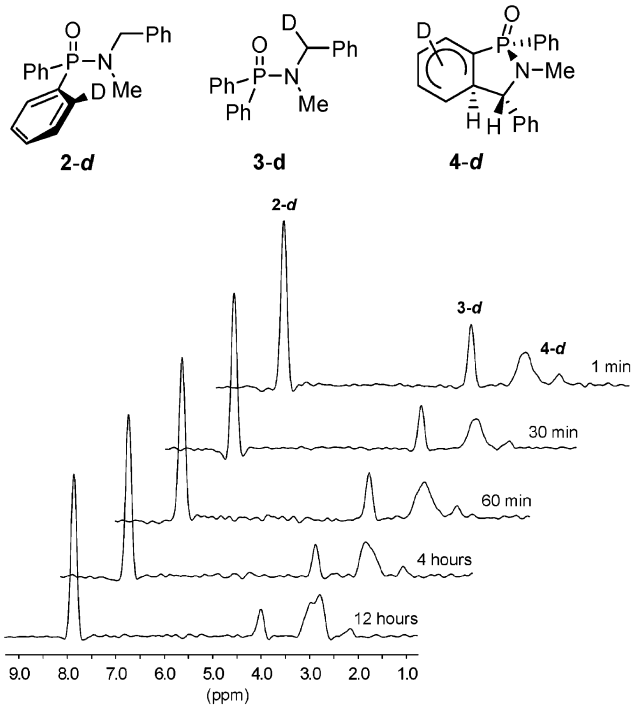


Figure 1. ^{2}H{^{1}H} NMR spectra (46.5 MHz) of the dearomatization−deuteration of **1** as a function of the metalation time t_1. Spectra measured from the crude product in $CDCl_3$ at room temperature.

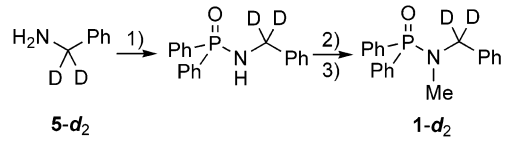
Table 1. Distribution of Products (%) in the Dearomatization−Deuteration of **1** at Increasing Time (t_1) Based on ^{2}H NMR Measurements[a]

t_1 (*s*-BuLi)	**2-*d***	**3-*d***	**4-*d***
1 min	36	15	49
30 min	37	12	51
60 min	38	10	52
4 h	35	8	57
12 h	33	7	60

[a] The concentration of **1** in the ^{1}H NMR spectra was below the detection level.

(23) The magnitude of $t_2 = 30$ min represents a value optimum for most of the protonating reagents used that takes into account solubility problems at the temperature of −90 °C. For simple alcohols, this time can be reduced to 1 min, as deduced from the decoloration of the reaction mixture.

Scheme 2 [a]



[a] (1) $Ph_2P(O)Cl$, Et_3N (2.5 equiv), toluene, −78 °C. (2) NaH (2.2 equiv), THF. (3) MeI (1.1 equiv), rt.

positions with respect to the phosphorus atom appear at δ = 2.97 and 2.85 ppm, respectively.

From the results in Table 1 we concluded that in the absence of coordinating agent, 49% dearomatization takes place by t_1 = 1 min. The yield of **4-*d*** increases to 60% with increasing t_1 at the expense of the ^{2}H-benzylic derivative **3-*d*** (i.e., the benzylic anion precursor). Curiously, the concentration of the ortho-deuterated compound **2-*d*** (i.e., the ortho-lithiated intermediate) remains practically constant (≈36%) within experimental error. In other words, the translocation is apparently inhibited in the absence of cosolvent. Therefore, the distribution of deuterated products also indicates that the ratio of ortho:benzylic lithiation of **1** achieved by *s*-BuLi is approximately 36:64.[24] Consequently, the direct lithiation at the benzylic position of **1** is favored by a factor of nearly 2 with respect to the ortho lithiation. The preferred lithiation α to the nitrogen atom of **1** is similar to the known preference for benzylic lithiation of *N*-benzylbenzamides.[25] In contrast, the lithiation−alkylation of *N*-benzyl-*N*-methyl(diphenyl)thiophosphinamides at low temperature in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) leads exclusively to products of ortho lithiation.[26]

In the presence of cosolvent the dearomatization of **1** and subsequent protonation with 2,6-di-*tert*-butyl-4-methylphenol yields **4** (E = H) almost quantitatively.[13] This fact suggests that either the translocation is accelerated by the action of the coordinating cosolvent or the cosolvent exclusively favors lithiation at the benzylic position. To check these hypotheses, we applied the optimized dearomatization−protonation sequence of reactions to the phosphinamide **1-*d*$_2$**, which is dideuterated at the benzylic position. Phosphinamide **1-*d*$_2$** was prepared in 84% overall yield in a three-step process involving the treatment of the doubly labeled benzylic amine **5-*d*$_2$** with diphenylphosphinoyl chloride in the presence of triethylamine (2.5 equiv) in toluene at −78 °C, metalation of the resulting phosphinamide with NaH in THF at room temperature, and addition of MeI (Scheme 2).[27]

If the lithiation of **1-*d*$_2$** took place exclusively at the benzylic position, then only the tetrahydrobenzazaphosphol **6-*d*** monodeuterated at the carbon linked to the phenyl substituent would be formed (Scheme 3). In contrast, the dearomatized products derived from an anionic translocation (i.e., **7-*d*$_2$**, **8-*d*$_2$**, and **9-*d*$_2$**) would exhibit a scramble of the deuterium label between all possible ortho positions with respect to the phosphorus atom (Scheme 3). The dearomatization−protonation of **1-*d*$_2$** under the same reaction conditions used for the unlabeled phosphinamide **1** afforded a mixture of **7-*d*$_2$**/**8-*d*$_2$**/**9-*d*$_2$** in a ratio of 1:1:2. The product distribution was established based on the integrals of the signals of H-3a, H-7, and H-10 in the ^{1}H NMR spectrum of the crude mixture (Figure 2). Compound **9-*d*$_2$** is derived from the attack of the benzylic anion on the nondeuterated *P*-phenyl ring containing two equivalent ortho positions. Consequently, twice as much **9-*d*$_2$** can be formed with respect to the other isomers. The statistical distribution of isomers obtained indicates that, as expected, there is no isotopic effect in the anionic cyclization step.

The assignments deduced from the proton spectrum were confirmed through the conventional ^{13}C and attached proton test (APT) NMR spectra of the crude product, the latter being optimized for the quantitative determination of quaternary carbons.[28] The integral measured for the signals of C-3, C-10, C-3a, and C-7 gave a ratio of 4:2:1:1. The magnitude of the coupling constants $^nJ_{CX}$ (X = ^{2}H, ^{31}P, n = 1, 2) measured from these spectra for the labeled carbons are summarized in Table 2. The absence of **6-*d*** suggests that the kinetic isotope effect inhibits the direct lithiation of **1-*d*$_2$** at the benzylic position. On the other hand, the statistical formation of **7-*d*$_2$**, **8-*d*$_2$**, and **9-*d*$_2$** reveals that anion translocation **I** → **II** (Scheme 1) is indeed possible and that the coordinating agents HMPA or DMPU catalyze the transformation by lowering the energy barrier of the process.

NMR Studies. We next attempted the structural characterization of anions **I**, **II**, and **III** by monitoring their formation reactions with NMR spectroscopy. Most of the NMR studies were carried out on a spectrometer operating at a proton frequency of 300 MHz. The information collected was complemented by data measured on a spectrometer of higher magnetic field (11.74 T, ^{1}H frequency of 500 MHz) recently purchased by the University of Almería (see Supporting Information), which allowed us to perform triple-resonance experiments involving the nuclei ^{1}H, ^{7}Li, and ^{31}P. For sake of clarity, these experiments will be discussed separately. The NMR samples of approximately 0.2 M in THF-d_8 were prepared under conditions analogous to those used in the bulk (see Experimental Section).[29] The only difference was that partial evaporation of the solvent from the *s*-BuLi hexane solution under reduced pressure at −20 °C was used to reduce the intensity of the unwanted hexane signals. The resulting *s*-BuLi was then dissolved in THF-d_8 (0.25 mL) and transferred to an NMR tube containing a solution of phosphinamide **1** in THF-d_8 (0.25 mL) at −90 °C. The effect of the cosolvent was studied on samples to which 6 equiv of dry HMPA was added prior to the metalation step. We first tackled the NMR structural study in the absence of coordinating agent as a result of the lower rate of the transformation of **1** into **III** when HMPA or DMPU is not present. The sample was transferred to the spectrometer at −90 °C, and then a series of ^{1}H, ^{31}P, and ^{13}C, ^{1}H DEPT135 NMR spectra were sequentially measured at increasing metalation time (t_1).[30] The spectra obtained are shown in Figures 3−5.

The proton spectrum measured in the first minute of reaction (Figure 3, t_1 = 1 min) exhibits signals corresponding to the

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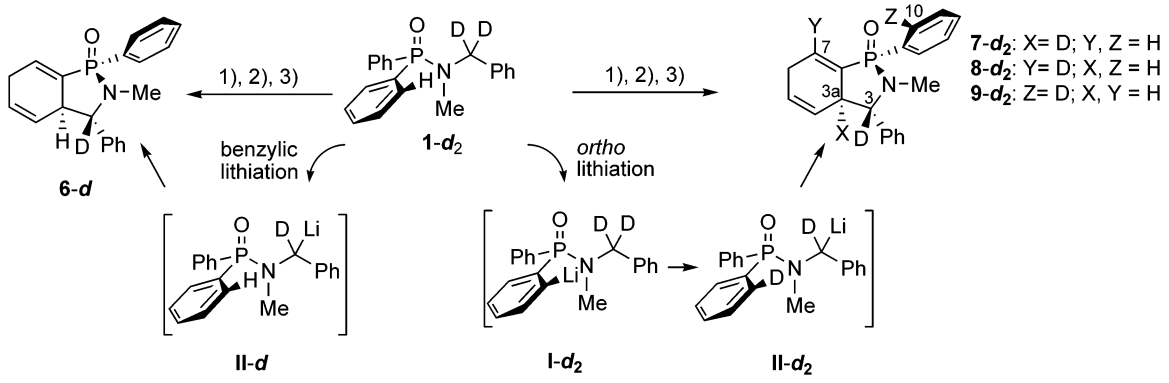
(27) The quantitative formation of the intermediate *N*-benzylphosphinamide was monitored by ^{31}P NMR spectroscopy of aliquots of the reaction.
(28) One-dimensional APT ^{13}C NMR optimized for quaternary carbons: repetition delay of 2 s, spin−echo time of $1/(2J_{CH})$ (J_{CH} = 145 Hz) 3.03 ms. Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.
(29) About five samples were examined in each spectrometer. They gave consistent and reproducible results. Among the variables analyzed, we evaluated the effect of cosolvent, concentration of base, temperature, and time of metalation.

Scheme 3 [a]



[a] (1) *s*-BuLi (2.5 equiv), DMPU (6 equiv), THF, −90 °C, 30 min. (2) 2,6-Di-*tert*-butyl-4-methylphenol, THF, −90 °C, 30 min. (3) H_2O.

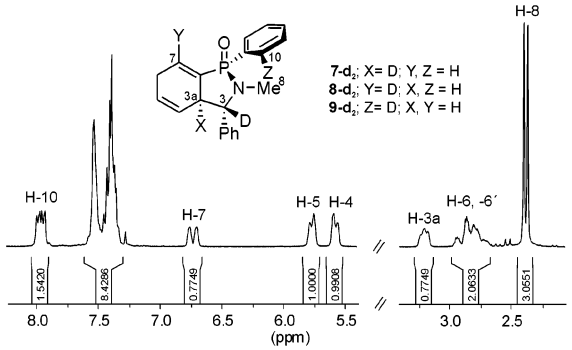


Figure 2. ^{1}H NMR spectrum (300.13 MHz) of the crude mixture of **7-*d*$_2$**, **8-*d*$_2$**, and **9-*d*$_2$** measured in $CDCl_3$ at room temperature.

Table 2. $^nJ_{CX}$ (Hz) for the Deuterated Carbons of **7-*d*$_2$**, **8-*d*$_2$**, and **9-*d*$_2$**

compd	$^1J_{CD}$ C−3	$^2J_{PC}$ C−3	$^1J_{CD}$ C−3a	$^2J_{PC}$ C−3a	$^1J_{CD}$ C−7	$^2J_{PC}$ C−7	$^1J_{CD}$ C−10	$^2J_{PC}$ C−10
7-*d*$_2$	10.6	32.4	18.8	14.0				
8-*d*$_2$	10.6	32.4			13.1	9.6		
9-*d*$_2$	10.6	32.4					10.6	36.2

starting phosphinamide **1** [δ 2.46 (3H, $^3J_{PH}$ = 11.3 Hz), 4.11 (2H, $^3J_{PH}$ = 6.4 Hz), 8.18 (4H)]. At t_1 = 13 min, all previous signals are broadened and new signals appear in the aromatic (H^{ortho} of *P*-phenyl rings, δ 7.96 and 8.34 ppm) and, most importantly, olefinic (δ 5.73 and 6.16 ppm) regions, which unequivocally arise from a dearomatized species. An additional signal at δ 4.25 ppm is overlapped with that of the methylene protons of **1** (δ 4.11 ppm). The intensities of the new signals increase with increasing t_1 at the expense of those of **1**. Therefore, the dearomatized species can be safely assigned as **III**, the precursor of the product isolated in the dearomatization−protonation of **1**.[31] When almost 1 h of reaction has elapsed (Figure 3, t_1 = 54 min), **1** is practically consumed. Two new *N*Me doublets appear at δ 2.23 ($^3J_{PH}$ = 8.7 Hz) and 2.54 ($^3J_{PH}$ = 11.3 Hz) ppm in the ratio of 1.4:1, and the olefinic region shows two new multiplets (δ 5.69 and 6.08 ppm) barely discernible at the base of the more intense one (approximate intensity ratio of 1:0.1). We assigned the latter set of new signals to a second dearomatized intermediate **IV**. On the other hand, the methylene group at δ 4.11 ppm evolves into three partially overlapped signals: multiplets at δ 4.08 and 4.23 ppm and a broad singlet at δ 4.17 ppm. An additional increase of the reaction time produced only minor changes (Figure 3, t_1 = 91 min), the most interesting being the observation of a third *N*Me doublet of low intensity at δ 1.92 ppm ($^3J_{PH}$ = 8.3 Hz) and a broad signal at δ 3.9 ppm. Significantly, the integral ratio of the *N*Me signals at δ 2.23 and 1.92 ppm is the same as that found for the two sets of olefinic multiplets (1:0.1). To summarize, the ^{1}H NMR study shows that the lithiation of **1** leads to the formation of two dearomatized intermediates **III**

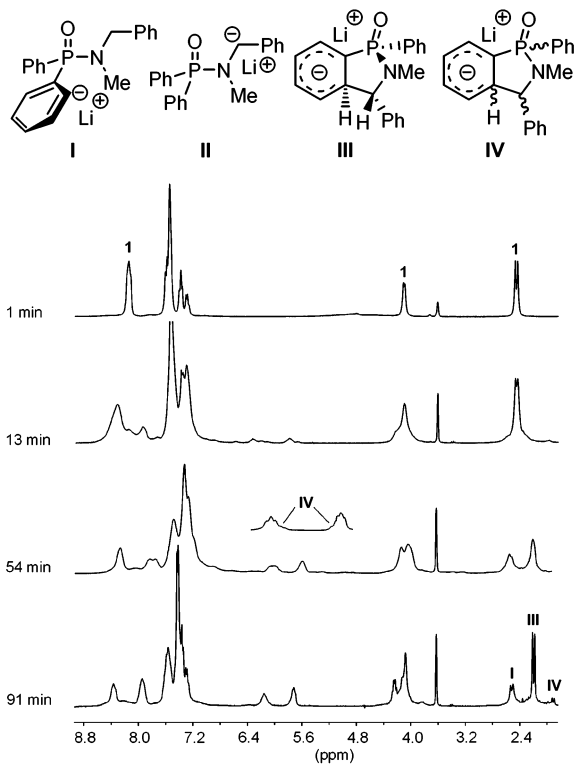


Figure 3. ^{1}H NMR spectrum (300.13 MHz) of the lithiation of **1** with *s*-BuLi as a function of t_1. General conditions: THF-d_8, −90 °C, 16 scans accumulated; total measuring time per spectrum of 1 min.

(30) Although the quaternary carbons are missing from the DEPT135 spectra, the repetition rate of the experiment is controlled by the relaxation time of the protons, which is shorter than those of the carbons. Therefore, a reasonable signal-to-noise ratio can be obtained from the DEPT in a shorter time than from a standard ^{13}C NMR spectrum. This is an important factor to obtain information about the early stages of the reaction, where the intervening species are being transformed throughout the measurement of the spectra.

(31) We assigned to species **III** the same relative configuration found for **4**, the product isolated in the dearomatization−protonation reaction, on the assumption that in the protonation the integrity of the stereogenic centers will not be affected. This assignment as well as that of species **IV** will be confirmed in the section discussing the sample prepared in the presence of HMPA.

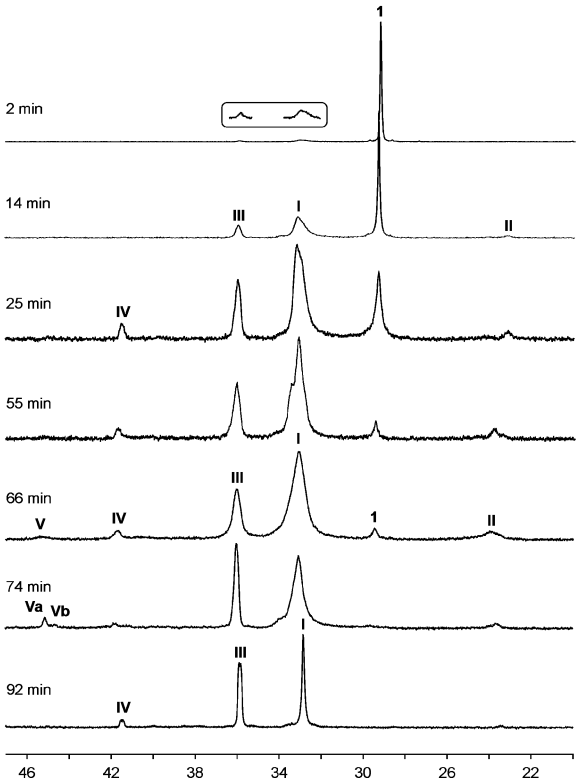


Figure 4. $^{31}P\{^{1}H\}$ NMR spectra (121.49 MHz) of the lithiation of **1** with *s*-BuLi as a function of t_1. General conditions: THF-d_8, −90 °C, 40−400 scans accumulated; total measuring time per spectrum of 1−11 min.

and **IV** in an approximate ratio of 1:0.1 plus a third species characterized by an *N*Me group at δ 2.54 and a broad singlet at δ 4.17 ppm.

The ^{31}P NMR spectra proved to be more informative in regard to the distribution of species in the reaction mixture owing to the higher dispersion of signals (Figure 4). In the first spectrum acquired (t_1 = 2 min), besides the signal of the starting phosphinamide **1** at δ 29.28 ppm, two new broad signals corresponding to **I** (δ 33.15 ppm) and **III** (δ 36 ppm) can be identified above the noise upon increasing the vertical scale. These two signals became clearly visible in the spectrum measured 12 min later. Moreover, the asymmetry of the signal labeled as **I** suggests that it, in fact, corresponds to two partially overlapped broad signals (δ 33.12 and 33.15 ppm). Additionally, a new broad signal **II** appears at δ 23.13 ppm. The intensity of the new species continues to grow with the consequent decreasing of **1** as the reaction progresses, except that of **II**, which decreases slightly. At t_1 = 25 min a new signal appears at δ 41.44 ppm corresponding to **IV**. Over the next 30 min a reequilibration between the species already present takes place (Figure 4, t_1 = 55 min): the phosphinamide **1** has practically disappeared, and the two overlapped signals assigned to **I** are now partially resolved due to the reduction of the intensity of the more deshielded one. Their actual chemical shifts are δ 33.1 and 33.39 ppm.[32] For t_1 = 66 min they collapse again into a broad and intense signal at δ 33.1 ppm. Interestingly, a very

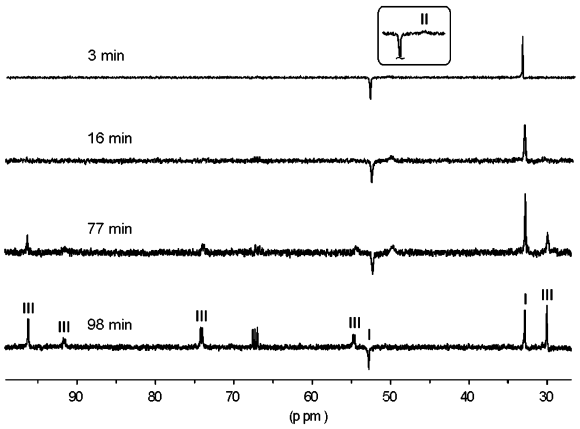


Figure 5. DEPT-135 NMR spectra (75.5 MHz) of the lithiation of **1** with *s*-BuLi as a function of t_1. General conditions: THF-d_8, −90 °C, 280−600 scans accumulated; total measuring time per spectrum of 3−31 min.

broad signal **V** begins to emerge at δ 45.38 ppm, which apparently splits into two sharper signals of unequal intensity at t_1 = 74 min (labeled as species **Va**/**Vb**). Finally, the steady state is reached at t_1 = 92 min. Similar to the proton spectrum, only species **I**, **III**, and **IV** remain in solution in a ratio of 1.2:1:0.1. Their respective ^{31}P chemical shifts are δ 32.85, 36.03, and 41.48 ppm. The assignment of the ^{31}P signals was readily achieved through the $^{1}H,^{31}P$ gHMQC spectrum optimized for the observation of phosphorus−proton long-range couplings (Figure S1, Supporting Information). The phosphorus of species **III** and **IV** correlated with olefinic protons, while the signal of **I** only showed correlations with aromatic and aliphatic protons.

The DEPT-135 spectra helped to clarify the type of intermediates formed during the process (Figure 5). As expected, the first spectrum acquired (t_1 = 3 min) was dominated by the signals of **1** [δ_C 32.76 (CH_3), 52.25 (CH_2)]. Nevertheless, an incipient signal of positive phase is observed at δ 49.8 ppm. This chemical shift is appropriate for a benzylic CH, and the only source available for this type of carbon is the benzylic anion **II**. The concentration of **II** increases slightly over the next 13 min and reaches a maximum at t_1 = 77 min. This last spectrum, measured just after the ^{31}P spectrum at t_1 = 66 min, afforded additional key information. Let us focus on the relatively intense signal of negative phase at δ 52.25 ppm. Considering that at this time the starting phosphinamide was practically consumed, this signal cannot be derived from the methylene carbon of **1**; it must arise from the analogous methylene carbon of an ortho-lithiated species such as intermediate **I**.[33] This conclusion implies that the carbons of the CH_2 groups of **1** and **I** absorb at the same chemical shift under the measuring conditions. The same arguments apply to the *N*Me signals of **1a**, **I**, and **II**, all of which coincide at δ 32.75 ppm. The remaining signals of the spectrum are assigned to the highest concentrated dearomatized species **III**. Again, the spectrum after reaching the steady state (Figure 5, t_1 = 98 min) shows no signals corresponding to compound **II**; only the signals for anions **I** and **III** are observed. The concentration of the second

(32) The slight variations of the chemical shifts are a consequence of the changes in the concentration of the different species in the reaction mixture with increasing t_1. The ^{31}P nucleus is very sensitive to these changes. Possible fluctuations of the temperature are considered negligible. Tebby, J. C. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis. Organic Compounds and Metal Complexes*; Verkade, J. G., Quin, L. D., Eds.; VCH: Weinheim, 1987; Chapter 1, pp 1−60.

(33) The structural elucidation and synthetic applications of ortho anions such as **I** is currently under study. To exclude complications derived from possible benzylic deprotonation we are using *N*,*N*-diisopropyldiphenylphosphinamide as the starting material. As suggested by a reviewer, the lithiation of **1-d_2** would be very informative also. We thank the referee for this suggestion. These results will be reported in due course.

dearomatized species **IV** was too low to be detected, even after the accumulation of 600 scans.

Variation of the concentrations of species **I** and **II** during the NMR study (Figure 4) and correlations observed in the $^{1}H,^{31}P$ gHMQC spectrum indicate that the benzylic anion **II** gives rise to only one signal at δ_P 23.13 ppm, whereas two ortho-lithiated species **I** are initially formed, giving signals at δ_P 33.1 and 33.39 ppm that evolve into a single signal at δ_P 32.85. More importantly, this study clearly shows that the benzylic and ortho anions are formed almost simultaneously, with an apparent preference for **I** (cf. ^{31}P NMR spectra at $t_1 = 2$, 14, 25, and 55 min). The benzylic anion **II** evolves through anionic cyclization to give the dearomatized anions **III** and **IV**, whereas the ortho-lithiated compound **I** remains in solution. Once all species equilibrated, integration of the ^{31}P NMR spectrum afforded a ratio of dearomatization:ortho lithiation of 57:43, which is in reasonable agreement with the ratio of 64:36 deduced from the deuteration reactions.[34] However, the relative concentration of **I** in the time period $t_1 = 14-74$ min is higher than that of the remaining anions. Given that the translocation from **I** to **II** in the absence of HMPA has been excluded through the labeling studies, we interpret the comparatively high intensity of **I** at intermediate t_1 values as the result of the formation of mixed aggregates of undefined structure between **I** and other anions present in solution. This hypothesis is supported by the broadening observed for the ^{31}P signal of **I** in the first hour of reaction. We tentatively assign a dimeric structure to **I** based on the recent characterization of ortho-lithiated *N*,*N*-diisopropylbenzamide as a dimer.[35] As the reaction progresses, the thermodynamically more stable species prevail in solution.

Prior to undertaking spectral assignment of compounds **I**, **III**, and **IV**, we increased the temperature of the sample from −90 to −70 °C in steps of 10 °C and measured the spectra at the new temperatures. This temperature modification was implemented for two reasons: (1) narrower signals may be expected due to the reduction of the viscosity of the sample, and (2) the equilibrium state between the species present in solution could be altered. To our delight, both effects were observed, thereby providing important structural and chemical information. Thus, increasing the temperature from −90 °C by 10 °C produced better separation of the olefinic signals of **III** and **IV** in the proton spectrum and an overall improvement of the resolution of all signals. Moreover, a small but measurable increase of the relative concentration of **IV** with the consequent reduction of that of **III** was noted. These trends became even more noticeable when the temperature was further increased to −70 °C. The new ratio of compound **III**:**IV** obtained by integration of the *N*Me signals is 1:0.17 (cf. 1:0.1 at −90 °C). Additionally, a doublet is clearly identified at δ 4.18 ppm ($^{3}J_{PH} = 5.7$ Hz), corresponding to the methylene protons of **I**. The existence of the phosphorus−proton coupling was confirmed through the $^{1}H\{^{31}P\}$ spectrum.

The changes in the ^{31}P NMR spectrum with the increase of temperature revealed even more information. Besides the reduction of the ratio **III**:**IV** already deduced from the ^{1}H spectrum, the narrowing of the signals revealed the existence of phosphorus−lithium-7 couplings. At −70 °C, the signals at δ 36.03 and 41.48 ppm split into quartets of $^{2}J_{(^{31}P^{7}Li)} = 6.4$ and 7.4 Hz, respectively. This means that each phosphorus nucleus is coupled to only one lithium nucleus, and therefore, the lithiated dearomatized compounds **III** and **IV** are both monomers (Figure 6). The detection of $^{2}J_{PLi}$ couplings is a well-known structural tool for the identification of the aggregation state of lithiated phosphoramides[36] and phosphonamides.[37] Reich et al. developed a very efficient methodology for studying the ion-pairing state of organolithium compounds through HMPA titration. The degree of HMPA coordination to lithium is deduced from the measured $^{2}J_{PLi}$ couplings.[38] Our results indicate that the P═O group of a phosphinamide also coordinates to a lithium atom with a magnitude of $^{2}J_{(^{31}P^{7}Li)}$ similar to those found in phosphoramides. Unfortunately, no $^{2}J_{(^{31}P^{7}Li)}$ coupling could be resolved for the phosphorus signal of the ortho anion **I**.[39]

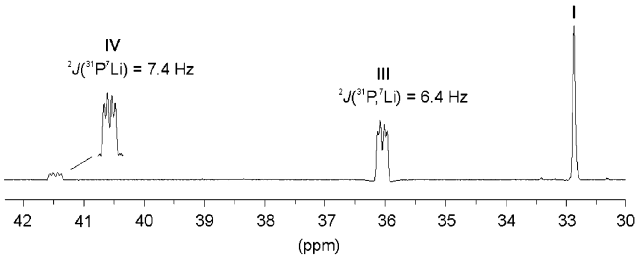


Figure 6. ^{31}P NMR spectrum (121.49 MHz) of the lithiation of **1** with *s*-BuLi measured at $t_1 > 2$ h in THF-d_8 at −70 °C. The FID was multiplied by a Gaussian of LB = −8 and GB = 0.04 prior to the Fourier transformation.

Raising the temperature to −70 °C had no significant effect on the ^{13}C NMR spectrum (i.e., the concentration of **IV** was still too low to be detected within a reasonable measuring time). The complete structural assignment of anions **I** and **III** was carried out at −70 °C based on the analysis of the $^{1}H,^{13}C$ gHMQC, and gHMBC spectra (Figures S2 and S3, respectively, Supporting Information). The gHMQC allowed us to identify the most relevant C−H pairs of nuclei of both compounds. For **I** these are limited to the CH_3 [δ_H 2.56 ppm ($^{3}J_{PH} = 11.3$ Hz); δ_C 32.75 ppm] and CH_2 [δ_H 4.18 ($^{3}J_{PH} = 5.7$ Hz); δ_C 54.26 ppm] of the amine moiety and the H^{ortho} of the *P*-phenyl rings [δ_H 8.34 ppm; δ 133.53 ppm ($^{2}J_{PC} = 9.4$ Hz)] (Figure S2, Supporting Information).

A selection of NMR data of **III** is given in Table 3. The dearomatized system is readily assigned through the correlations

(34) Some possible reasons for the difference observed are the higher concentration of the NMR sample with respect to the standard reaction and most probably the imprecision of the integration of broad signals due to the reduction produced by short transverse relaxation times of different nuclei.

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(39) One may reasonably assume that in this anionic species the P═O linkage will coordinate to the lithium cation, leading to a possible scalar coupling via $^{2}J(^{31}P^{7}Li)$. However, if this coupling exists it must be smaller than the resolution achieved in the experiment.

Table 3. Selection of NMR Data of **III** Measured in THF-d_8 at −70 °C[a]

C/H	δ_H	$^nJ_{PH}$	δ_C	$^nJ_{PC}$
3	4.05		75.89	17.9
3a	4.05	*b*	56.19	17.4
4	4.12	4.6	98.28	5.2
5	5.69		129.90	s
6	4.24	7.7	93.66	15.1
7	6.14	8.4	133.85	16.0
7a			67.32	143.9
9			143.40	133.8
10	7.94	*b*	134.82	7.5
13			145.75	10.4

[a] δ in ppm, J in Hz. [b] Not measured due to partial signal overlap.

of the olefinic methyne groups. As expected, the sp^3 carbon C3a absorbs at the highest field. The delocalization of the negative charge through carbons C4 and C6 produced a large upfield shift [$\Delta\delta$(**III-4**) = −24.5 ppm for C4] (**4**, R^1 = Me, E = H, Scheme 1), whereas carbons C5 and C7 are much less affected [$\Delta\delta$(**III-4**) = 4.5 ppm for C5 and −1.7 ppm for C7]. The quaternary carbon C7a was identified based on the correlations observed in the gHMBC spectrum with H3a (Figure S3, Supporting Information). For this correlation four cross peaks are obtained due to the passive coupling to ^{31}P either during the evolution ($^1J_{PC}$) or acquisition time ($^2J_{PH}$). Moreover, the negative slopes of the cross peaks indicate that both couplings are of opposite relative sign. Considering that in P(V) compounds $^1J_{PC}$ is always positive,[40] it follows that $^2J_{PH}$ is negative. On the other hand, the correlation of H3 with C4 facilitates the unequivocal assignment of C4 and, by default, C6. Regarding the stereochemistry of **III**, we tentatively assumed that the stereochemistry of the product of the dearomatization−protonation sequence **4** reflects the stereochemistry of the major component of the mixture (i.e., **III**). Although in light of the Curtin−Hammett principle this is not necessarily true, this assumption was later confirmed (see below). Significantly, carbon C6 shows the widest ^{13}C NMR signal ($W_{1/2}$ = 46 Hz); this is the position generally attacked by most of the electrophiles used to trap the dearomatized species of **1**. The increased signal width may be explained by the proximity of the quadrupolar lithium-7 nucleus, which causes an increase in the transverse relaxation rate[41] This feature suggests that the lithium cation is most probably η^3-coordinated to the C6−C7−C7a moiety of the dearomatized six-membered ring anion. The dissymmetry of the coordination would be forced by the coordination of the P═O group to the lithium atom, as deduced from the phosphorus−lithium-7 coupling constant measured. Also noteworthy is the large increment of $^1J_{PC}$ experienced by C7a [Δ^1J_{PC}(**III-4**) = 23.2 Hz]. Such effects on $^1J_{PC}$ upon metalation have been previously noted in other phosphorus-stabilized anions.[42]

To summarize the NMR results discussed above, the study of the lithiation of **1** in the absence of coordinating cosolvent showed the presence of at least five intermediate species, **I**−**V**: the ortho anion **I** (presumably a dimer), the benzylic anion

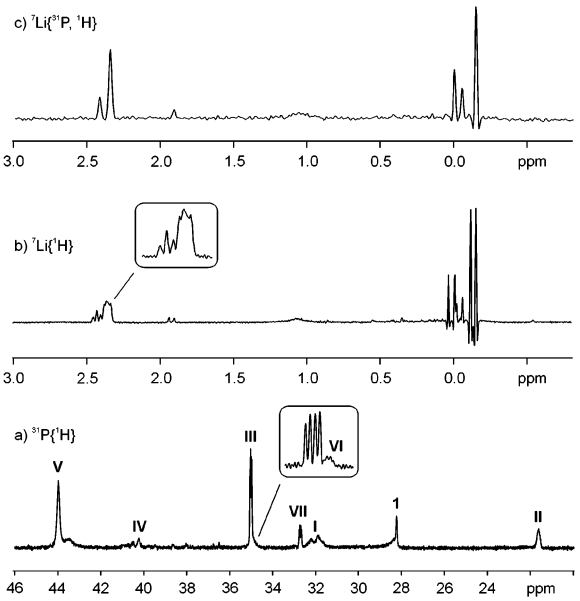

Figure 7. NMR spectra of the earlier stages in the lithiation of **1** with *s*-BuLi at −110 °C in THF-d_8. (a) ^{31}P{^{1}H} (202.46 MHz), including expansions of **III** and **VI**; (b) ^{7}Li{^{1}H} NMR (194.37 MHz), including expansions of **V**; and (c) ^{7}Li{^{31}P,^{1}H}. In all cases Gaussian multiplication of the FID (LB = −2, GB = 0.14 for ^{31}P and LB= −4, GB= 0.24 for ^{7}Li) was performed prior to the Fourier transformation.

II, the monomeric dearomatized compounds **III** and **IV,** and the unknown species **V**. No translocation from **I** to **II** was observed, in agreement with the labeling studies. The anions **I** and **III** were fully characterized. In the first case, only one isomer persisted when the steady state was reached at −70 °C. Similar to **III**, compound **IV** also forms a monomeric contact ion pair. However, the low concentration of **IV**, and in the case of **II** its short lifetime, impeded complete structural characterization. No information about the aggregation state of benzylic anion **II** and the species labeled as **V** could be obtained.

^{7}Li,^{31}P Shift Correlation. Triple-resonance experiments were carried out on a NMR spectrometer working at a proton frequency of 500 MHz. A fresh 0.2 M sample in THF-d_8 was prepared, and the ^{31}P and ^{7}Li NMR spectra were measured at −90 °C. Due to the larger spread of frequencies available, species that at 300 MHz are in the fast-exchange regime on the NMR time scale (giving rise to an average signal) might now be observed as individual components at the higher field of 500 MHz. This proved to be the case as can be seen in the ^{31}P NMR spectrum shown in Figure 7a (cf. Figures 4 and S4, Supporting Information).[32] The excess of *s*-BuLi is clearly established in the ^{1}H NMR spectrum by the signal of the lithiated methine group at δ −0.89 ppm (Figure S5, Supporting Information). The signals assigned to the ortho anion **I** (probably mixed aggregates and/or stereoisomeric dimers) are very broad and of

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relatively low intensity, whereas the concentration of the two species **Va**/**Vb** is rather high. The signal intensities and line widths of **Va** and **Vb** are different. In addition, two new species, **VI** and **VII**, characterized by 1:1:1:1 quartets at δ 34.9 [$^2J_{(^{31}P^7Li)}$ = 4.4 Hz] and 32.7 ppm [$^2J_{(^{31}P^7Li)}$ = 7.7 Hz], respectively, are observed (Figure 7a). This multiplicity, together with the new signals appearing in the olefinic region of the ^{1}H NMR spectrum (Figure S5, Supporting Information), suggests that **VI** and **VII** are two new monomeric dearomatized anion stereoisomers of **III** and **IV**. Considering that in the dearomatization of **1** three new stereogenic centers are formed, the dearomatized anions **III**, **IV**, **VI**, and **VII** represent all possible diastereomers that could be obtained in the reaction. Compounds **VI** and **VII** are relatively unstable, and with time they evolve into the more stable isomers **III**/**IV**. It is noteworthy that in the dearomatization−electrophilic trapping of **1a** small amounts of products derived from anions other than **III** and **IV** have been occasionally isolated.[17] The time and temperature evolution of the sample (Figure S4, Supporting Information) shows the same features observed in the sample previously measured at lower frequency (Figure 4). Thus, at −70 °C only anions **I**, **III**, and **IV** are present in solution.

The ^{7}Li NMR study was conducted on a freshly prepared 0.2 M sample. For simplicity, in this case an equimolecular ratio of base and substrate was used. In the earliest stages of the deprotonation reaction, a significant amount of free phosphinamide **1** (δ 28.22 ppm) is still visible in the ^{31}P NMR spectrum (Figure S6, Supporting Information). The ^{7}Li NMR spectrum measured at −90 °C exhibits up to seven signals: three doublets, two poorly resolved triplets, and two very broad singlets. Lowering the temperature to −110 °C allowed us to resolve all multiplets except a broad signal at 1.07 ppm (Figure 7b). The doublets at δ −0.13 ppm, $^2J_{(^{31}P^7Li)}$ = 6.9 Hz; −0.04 ppm, $^2J_{(^{31}P^7Li)}$ = 7.8 Hz; 0.01, $^2J_{(^{31}P^7Li)}$ = 4.5 Hz; and 1.92 ppm, $^2J_{(^{31}P^7Li)}$ = 6.6 Hz are clearly observed. The multiplets at δ 2.36 and 2.43 ppm were identified, respectively, as a double doublet [$^2J_{(^{31}P^7Li)}$ = 4.0, $^2J_{(^{31}P^7Li)}$ = 5.5 Hz] and a triplet [$^2J_{(^{31}P^7Li)}$ = 5.0 Hz] from the ^{7}Li{^{31}P, ^{1}H} spectrum (Figure 7c).

The connectivity between the ^{7}Li,^{31}P spin pairs was readily obtained through the ^{7}Li,^{31}P{^{1}H} HMQC spectrum[43] recorded at −110 °C (Figure 8).[44] The assignments made are given in Table 4. The correlations arising from the dearomatized monomeric species indicate that the pairs of ^{31}P and ^{7}Li signals corresponding to anions **III** and **VI** are completely overlapped. In contrast, those derived from **IV** and **VII** are well separated. Most importantly, the ^{31}P signal of the benzylic anion (δ 21.21 ppm) correlates with the lithium doublet at δ 0.01 ppm, a multiplicity consistent with a monomeric structure. Monomeric lithium benzylic anions adjacent to a nitrogen atom, which are dipole-stabilized by a carbonyl moiety, have been characterized both in the solid state[45] and solution.[46] We recently demonstrated that lithiation of phosphinamide **1** with *s*-BuLi in diethyl ether

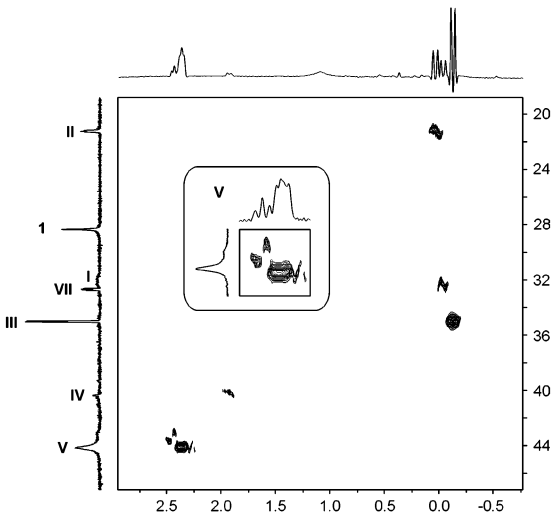

Figure 8. 2D ^{7}Li,^{31}P{^{1}H} HMQC NMR (194.37 MHz) of the earlier stages in the lithiation of **1** with *s*-BuLi at −110 °C in THF-d_8. The inset represents the correlation detected for the species **Va**/**Vb**. Experiment started at a metalation time of 2 min. Total measuring time: 2 h 40 min.

Table 4. ^{31}P (202.46 MHz) and ^{7}Li (194.37 MHz) NMR Data of Anions **I**−**VII** Measured in THF-d_8 at −110 °C[a]

data	I[b]	II	III	IV	Va	Vb	VII
δ (^{31}P)	31.92, 32.22	21.21	34.97	40.32	44.12	43.16	32.66
δ (^{7}Li)	1.07	0.01	−0.13	1.92	2.36	2.43	−0.04
$^2J_{PLi}$	bs[c]	4.5	6.9	6.6	4.0, 5.5	5.0	7.8

[a] δ in ppm, J in Hz. [b] Mixed aggregate and/or stereoisomeric dimers (see text). [c] Broad singlet.

takes place exclusively at the benzylic position, and the resulting anion is stabilized by forming dimers containing either $(LiC)_2$ or $(LiO)_2$ four-membered rings.[43] Not unexpectedly, the broad ^{7}Li signal at δ 1.07 ppm is the only one that does not show any ^{31}P correlation. Its large signal width implies rapid transverse relaxation, and thus, the transverse magnetization generated at the beginning of the pulse sequence is completely lost during the delays involved in the experiment. It can be assumed that this lithium signal corresponds to the ortho anions **I** exhibiting broad singlets in the ^{31}P NMR spectrum. At −70 °C, the temperature at which the ortho anion produces a sharp ^{31}P singlet, all lithium signals collapse to an uninformative broad singlet. Further work is in progress to elucidate the structure of diphenylphosphinamides exclusively lithiated at the ortho position.[33]

The correlations of **Va** (δ 43.16 ppm) with the ^{7}Li triplet at δ 2.43 ppm and **Vb** (δ 44.12 ppm) with the ^{7}Li double doublet at δ 2.36 ppm are especially interesting. The reaction pathway for the transformation of **1** into compounds **2**, **3,** and **4** (Scheme 1) involves ortho, benzylic, and dearomatized anions that have already been identified. On the other hand, the presence of mixed aggregates resulting from coordination of the starting material **1** to any $\mathbf{Li^+1^-}$ species can be ruled out because the ^{31}P NMR spectrum should show two very distinct signals of equal intensity, which is not the case. Consequently, any other intervening anionic species should precede the deprotonation reaction; in other words, the phosphorus signals **Va** and **Vb** can be considered to arise from two pre-lithiation complexes formed between the phosphinamide **1** and *s*-BuLi. Taking into account that the organolithium base used has a stereogenic center, the multiplicity of the lithium signals reveals that the

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(44) At this temperature the intensity of the signals corresponding to species **I** decreased so much that they are only barely distinguishable above the noise in the resolution-enhanced ^{31}P NMR spectrum (Figure S6, Supporting Information). Additionally, the signals of the dearomatized anions **III** and **VI** are completely overlapped.
(45) Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887.
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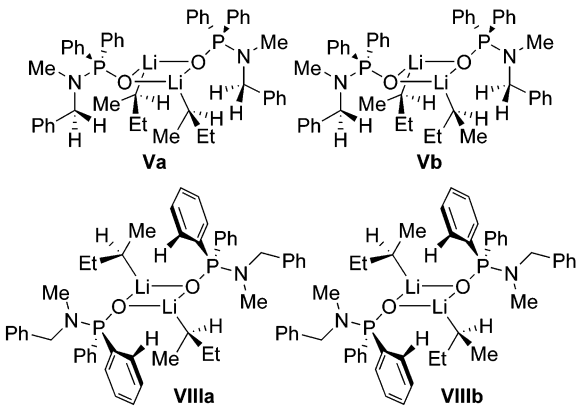
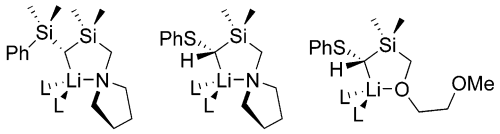
Chart 1. Structure of Precomplexes Preceding the Deprotonation Reactions of **1**



rate of stereochemical inversion at the carbanion center is slow on the NMR time scale.[47] The observation of slow inversion at the chiral center of *s*-BuLi is in accord with previous work showing that *s*-BuLi exists in cyclopentane solution as a mixture of diastereomeric dimers, tetramers, and hexamers that invert slowly at the lithiated carbon.[48] The splitting of the ^{7}Li signals of **Va**/**Vb** is consistent with a dimeric structure most probably constructed around an $(LiO)_2$ core in which the carbanionic and phosphorus-bearing substituents occupy opposite faces of the Li−O−Li−O four-membered ring (Chart 1).[49] Thus, the ^{31}P and ^{7}Li nuclei of **Va**, in which the two slowly inverting *s*-Bu moieties are of *like* configuration, are homotopic, and accordingly, a triplet is observed in the ^{7}Li NMR spectrum. On the other hand, under slow configurational inversion conditions, the ^{31}P nuclei of dimer **Vb** with two *s*-Bu moieties of *unlike* configuration are diastereotopic, whereas the ^{7}Li nuclei are enantiotopic. Consequently, the ^{7}Li NMR spectrum should consist of one signal that could exhibit two different ^{31}P,^{7}Li couplings. Indeed, this is the case, as demonstrated by the double doublet at δ 2.36 that collapses to a singlet upon ^{31}P decoupling (Figure 7c). Not unexpectedly, the ^{31}P NMR spectrum shows only a broad ^{31}P signal for each dimer. At the temperature of the measurement, two slowly exchanging ^{31}P signals of very similar chemical shift that are additionally split into 1:2:3:4:3:2:1 septets due to coupling to two ^{7}Li nuclei would give rise to an unresolved broad signal. It is important to point out that the acquisition of the ^{7}Li spectrum under simultaneous ^{31}P decoupling proved to be crucial to identifying the multiplicity of the ^{7}Li signal of **Vb**. Although the difference between the resonance frequencies of the two nuclei is only 8 MHz, the experiment can be routinely performed by using appropriate selective frequency filters. Furthermore, this single datum allowed us to distinguish **Va** and **Vb** from the corresponding stereoisomers having a trans arrangement for the pair of carbanionic and phosphinamide substituents **VIIIa**/**VIIIb** (Chart 1). The ^{31}P and ^{7}Li nuclei of complex **VIIIa** with *s*-Bu groups of *like* configuration will be diastereotopic, and those of the diastereomer **VIIIb** bearing *unlike* *s*-Bu groups will be enantiotopic. Therefore, three different ^{7}Li signals should be observed, which is not the case. The preference for the formation of **Va**/**Vb** versus isomers **VIIIa**/**VIIIb** may be assigned to steric interactions. The vicinal substituents of the four-membered ring of **Va**/**Vb** are in a trans configuration, and the ring may adopt a puckered conformation that minimizes the through-space interaction between substituents in relative positions 1 and 3. In contrast, the bulky phosphorus-containing and *s*-Bu moieties of **VIIIa**/**VIIIb** are in a cis configuration; thus, steric repulsions would disfavor this type of dimer.[50]

Chart 2. Chiral Lithium Chelates



Complex **Vb** is an anionic system with diastereotopic ^{31}P nuclei of two phosphorus(V) Lewis base ligands owing to a slowly inverting stereogenic carbanion center. The only related examples are the chelate organolithium compounds **10**−**12** reported by Reich et al. in which diastereotopic HMPA groups have been detected by NMR (Chart 2).[51] One mixed *s*-BuLi/lithium *N*-isopropyl-*O*-methyl valinol aggregate consisting of 1 equiv of *s*-BuLi and 2 equiv of lithium amide has been characterized in the solid state.[52] Mixed aggregates of *s*-BuLi with 3-methoxypropyllithium (tetramers)[53] and $LiBu^{s}Me_2SiO$ [$x LiBu^{s}$, $(6-x)LiBu^{s}Me_2SiO$; ($x = 1-4$)][54] have been identified in solution by NMR spectroscopy. Evidence for the involvement of precomplexes in the deprotonation of organic compounds by organolithium bases directed by functional groups bearing lone pairs (CIPE) is also limited.[55] This is the first time that pre-lithiation complexes have been structurally identified in the directed deprotonation of a phosphorus-bearing substrate. As the metalation progresses, complexes **Va** and **Vb** are consumed. Analogous to the sample measured in the spectrometer of lower magnetic field, when the temperature is raised to −70 °C a steady state is reached in which the only anionic species remaining in solution are **I**, **III,** and **IV** in a ratio of 1:0.77:0.04.

The results of the NMR study allow us to unravel the details of the mechanism of the anionic dearomatization of **1** in the

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(48) Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 254.
(49) Alternative structures based on dimers of *s*-BuLi with a C_2Li_2 core in which the lithium atom is additionally coordinated to phosphinamide **1** can be reasonably discarded. The similar magnitude of the ^{31}P,^{7}Li couplings of **Va**/**Vb** is consistent with the existence of static rather than fluxional aggregates. Therefore, species containing one and two molecules of **1** should be present to explain the observed ^{7}Li multiplicity. For such a mixture of aggregates a larger number of ^{31}P signals than those experimentally observed would be expected.
(50) The presence of these types of precomplexes cannot be completely discarded. The ^{31}P NMR spectrum shows a few signals that could not be assigned due to their very low intensity.
(51) Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 273.
(52) Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693.
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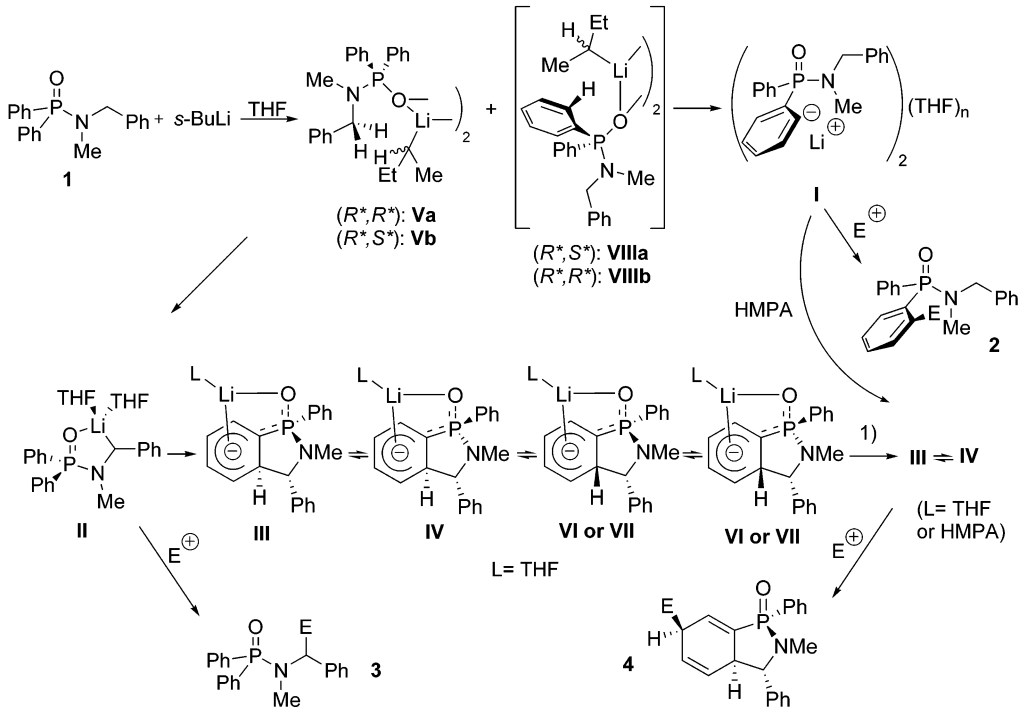
Scheme 4. General Mechanisms of the Anionic Dearomatization of **1**



absence of coordinating cosolvents (Scheme 4). The first step is the precomplexation of the base by the phosphinamide, which leads to the formation of two diastereomeric dimers, **Va** and **Vb**, in a ratio of 3:1. In these complexes, the proximity of the carbanion center of *s*-BuLi to the benzylic protons of the phosphinamide ligand promotes the deprotonation to give monomer **II**. This new anion is relatively unstable and undergoes intramolecular attack at the ortho position of each *P*-phenyl ring to afford all four possible stereoisomers of the dearomatized species **III**, **IV**, **VI,** and **VII** in a ratio of 1:0.07:0.13:0.25. These anions are in equilibrium, and as the reaction progresses the equilibrium shifts in favor of the thermodynamically more stable species **III** and **IV** (in the ratio of 10:0.06). On the other hand, ortho-lithiated anions **I** (presumably dimers) are present in the reaction right from the first measurements. Although they coexist with significant amounts of precomplexes **Va** and **Vb**, their concentration is not time dependent. Consequently, complexes **Va** and **Vb** do not participate in the ortho-deprotonation reaction. Considering that the surface containing the Li−O−Li−O four-membered ring and the phosphorus atoms of **Va** and **Vb** should be rather flattened, the evolution of these precomplexes exclusively toward anion **II** indicates that they adopt a preferred conformation where the benzylic protons are proximate to the carbanion center (Chart 1). Apparently this feature suggests that, in sharp contrast to carboxamides,[55c] the ortho lithiation of **1** is a kinetically driven process[22] that does not involve a CIPE mechanism. A more reasonable explanation is to assume that the ortho anions **I** are formed through the intermediate precomplexes **VIIIa** and **VIIIb**. As already mentioned, these complexes suffer from unfavorable steric interactions due to the cis arrangement of the *s*-Bu moiety and the phosphorus-bearing substituent of the $(LiO)_2$ ring. Molecular models show that to minimize steric effects, the *s*-Bu and *N*-benzylic fragments should be kept away from each other (Chart 1). In this conformation the carbanion center lies very close to the *P*-phenyl rings, enabling the deprotonation. Complexes **VIIIa** and **VIIIb** are thermodynamically disfavored, but they could be generated under kinetic control. Once formed, they would be too reactive to be detected, leading immediately to the ortho-metalated species **I**. The fact that the concentration of **I** remains practically constant implies that complexes **Va** and **Vb** do not equilibrate with **VIIIa** and **VIIIb** by virtue of a large energy barrier of interconversion. Complex-induced proximity effects in benzylic lithiation directed by amide-type functional groups have been reported previously.[55f,h,56] To our knowledge, this is the first time that the operation of the CIPE model has been demonstrated in the ortho- and benzylic-directed deprotonation of a phosphinamide. Unfortunately, all attempts to grow crystals of these anions suitable for X-ray studies were unsuccessful.

Deprotonation of 1 in the Presence of HMPA. We performed an analogous NMR study on the sample containing an excess of HMPA. As expected, the additive accelerates the transformation of **1** into dearomatized species. The first ^{31}P NMR spectrum acquired at −90 °C (t_1 = 2 min) showed only four signals. The signals corresponding to the two most deshielded phosphorus atoms were readily assigned to the dearomatized species **III** (δ 35.04 ppm) and **IV** (δ 39.8 ppm) and occurred with a ratio of 1:0.6. The most intense signal results from free HMPA (δ 25.18 ppm), and a broad one centered at δ 25.7 ppm is assigned to the HMPA coordinated to the lithium cations of **III** and **IV** (Figure 9). The splitting of the phosphorus signal of each anion into a quartet of intensity 1:1:1:1 again provides evidence for their monomeric nature.[57] The increase of the concentration of **IV** with respect to the sample prepared in the absence of HMPA allowed its spectroscopic characterization. For that purpose, we acquired the same set of NMR spectra

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(57) In our first report (see ref 10a) we assigned the lowest-field signal to a solvent-separated ion pair based (SIP) on the ^{31}P NMR spectrum (121.44 MHz) of a 0.158 M sample measured in THF-d_8 at −90 °C. Under these conditions the $^2J_{(^{31}P^7Li)}$ could not be resolved. Clearly, the lack of multiplicity is not a consequence of SIP structure but a concentration effect.

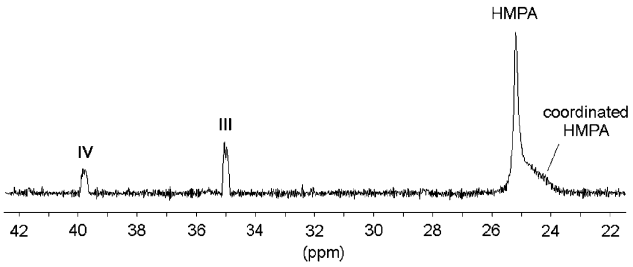


Figure 9. $^{31}P\{^{1}H\}$ NMR (121.49 MHz) spectrum of the lithiation of **1** with *s*-BuLi in the presence of HMPA, measured at $t_1 = 2$ min and −90 °C. The FID was multiplied by a Gaussian of LB = −6 and GB = 0.08 prior to the Fourier transformation.

Table 5. Selection of NMR Data of **IV** Measured in THF-d_8 at −70 °C in the Presence of HMPA[a]

C/H	δ_H	δ_C	$^nJ_{PC}$
3	3.90	81.29	14.7
3a	3.76	52.36	19.3
4	3.90	95.71	5.6
5	5.64	129.38	S
6	4.19	92.50	14.7
7	5.97	134.47	12.7
7a		62.43	164.8
9		141.36	114.5
10	7.99	136.01	7.1
13		145.53	6.6

[a] δ in ppm, J in Hz.

used for the structural assignment of **I** and **III**. The results of the analysis of these spectra are given in Table 5. Comparison of the NMR data of **III** and **IV** indicates that both have very similar structures. Significantly, the largest differences correspond to the magnitudes of $^1J_{PC}$. Thus, the phosphorus−carbon coupling of the *ipso* carbon C9 is 20 Hz larger in **III** than in **IV**, whereas the opposite occurs for C7a, Δ^1J_{PC}(**III**−**IV**) = −21 Hz. These findings suggest that compounds **III** and **IV** may differ in the relative configuration of the phosphorus atom. This is a reasonable suspicion considering that the two *P*-phenyl rings of the benzylic anion **II** are diastereotopic, and therefore, the anionic cyclization by attack at the *pro-R* or *pro-S* phenyl ring would provide two dearomatized species epimeric at the phosphorus center.

This hypothesis was supported by the 2D ROESY spectrum measured at −70 °C (Figure S7, Supporting Information). In both compounds a correlation is observed between H3a and the ortho protons of the phenyl ring adjacent to the nitrogen, indicative of their syn arrangement. Unfortunately the correlations involving the *P*-phenyl rings could not be unraveled due to signal overlaps. If the relative configuration of C3 and C3a is the same in both compounds, the difference must arise from the configuration of the phosphorus atom. However, the problem of assigning the correct *P*-configuration of **III** and **IV** remains unresolved. The ROESY spectrum also confirmed the coordination of HMPA molecules to the lithium through the correlations of the methyl protons with H3, H5, H7, and aromatic protons. Additionally, the lower intensity of the correlation with H5 relative to that of H7 supports the η^3 coordination of the lithium to the dearomatized ring proposed above.

Additional evidence of HMPA coordination to the dearomatized complexes was obtained through $^7Li,^{31}P$ shift correlation spectroscopy. To avoid the presence of the intense signal produced by the excess HMPA, a sample with an *s*-BuLi:**1**:HMPA ratio of 1.5:1:1 was prepared. The ^{31}P spectrum measured at −110 °C consisted of a mixture of dearomatized anions **III**, **IV,** and **VII** and at least four HMPA complexes absorbing in a narrow region (24.1−24.6 ppm). Two 1:1:1:1 quartets resulting from $^7Li,^{31}P$ couplings were clearly observed in this region. However, broadening effects and partial overlap impeded the determination of the precise number of species present (Figure S8a, Supporting Information). Fortunately the ^7Li spectrum did not suffer from these effects. The major signals were readily identified as three triplets (δ −0.51 ppm, $^2J_{PLi}$ = 10.8 Hz; δ −0.13 ppm, $^2J_{PLi}$ = 7.6 Hz; δ −0.02 ppm, $^2J_{PLi}$ = 8.8 Hz) and one quartet (δ −0.43 ppm, $^2J_{PLi}$ = 9.4 Hz). The assignment of the multiplicity was assisted by the $^7Li\{^{31}P,^{1}H\}$ spectrum (Figure S8b,c, Supporting Information). The $^7Li,^{31}P\{^{1}H\}$ HMQC spectrum showed that each one of the two lowest-field lithium triplets (δ −0.13 and −0.02 ppm) correlates with a pair of phosphorus nuclei corresponding to one HMPA molecule and one dearomatized anion; that is, the coordination sphere of lithium in the dearomatized anions is completed through binding to one HMPA molecule (Figure 10). The remaining ^7Li triplet (δ −0.51 ppm) and quartet (δ −0.43 ppm) correlate exclusively with HMPA signals, indicating that these multiplets originate from the respective coordination of two and three molecules of the phosphorus ligand to the lithium cation. Curiously, the ^{31}P signals of these complexes appear completely overlapped.

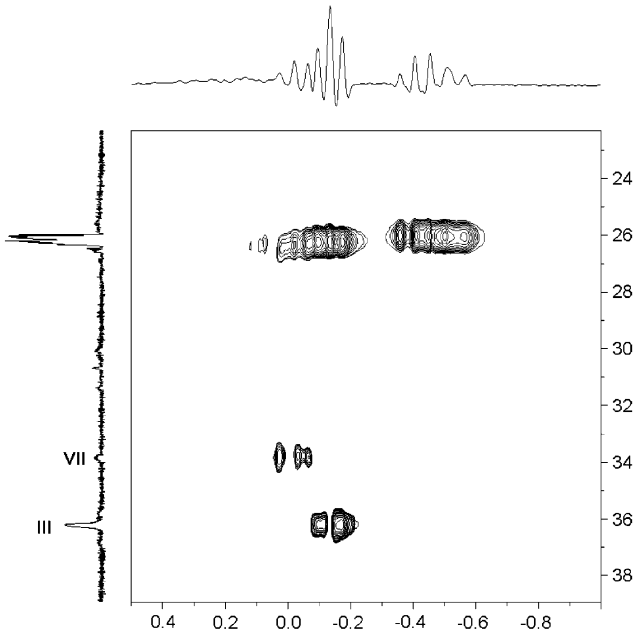
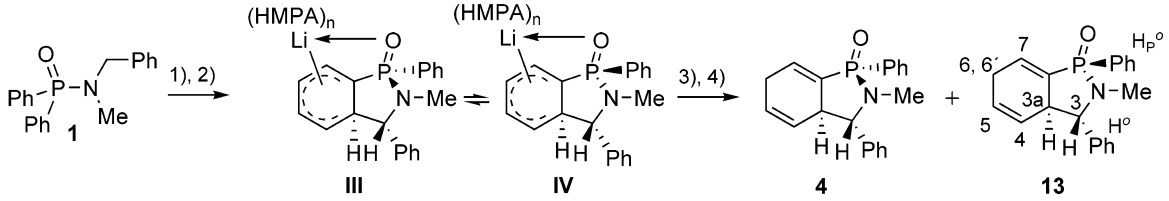


Figure 10. 2D $^7Li,^{31}P\{^{1}H\}$ HMQC spectrum(194.37 MHz) of a sample with a ratio *s*-BuLi:**1**:HMPA of 1.5:1:1, measured at −110 °C in THF-d_8.

The unequivocal assignment of the structures **III** and **IV** was achieved in two ways. We reasoned that if the concentration of **IV** in the sample prepared in the absence of cosolvent increased with increasing temperature, a similar effect could occur when HMPA is present. The temperature dependence of the relative ratio of **III**:**IV** could be anticipated based on the known reversibility of the anionic cyclization step and the possibility of obtaining products of kinetic or thermodynamic control.[17] Indeed, the ratio **III**:**IV** practically equalizes when the temperature of the sample is raised from −90 to −10 °C, and this product distribution remains unaltered when the temperature is

Scheme 5 [a]



[a] (1) *s*-BuLi (2.5 equiv), HMPA (6 equiv), THF, −90 °C, 30 min. (2) 60 min, −30 °C. (3) 2,6-Di-*tert*-butyl-4-methylphenol, −90 °C, 30 min. (4) H_2O.

decreased again. Interestingly, at temperatures close to 0 °C the anions revert quantitatively to the starting phosphinamide **1**, most probably by deprotonation of the solvent. A similar concentration variation is observed when the sample without additives is heated from −80 to −10 °C. The final ratio **III**:**IV** obtained is 55:45 (Figure S9, Supporting Information). These results indicate that **III** is the precursor of the kinetic product **4** (E = H, Scheme 4), and **IV** is the precursor of the thermodynamic product **13** (Scheme 5). On this basis, it can be safely affirmed that the configuration of the phosphorus atom of **III** must be the same as that in **4**. Consequently, the *P*-phenyl ring of **IV** is arranged anti to H3a and the phenyl substituent linked to C3.

The equilibration between **III** and **IV** suggested the possibility of isolating both diastereoisomers. With this aim in mind, we performed the dearomatization of **1** in the usual way (addition of 2.5 equiv of *s*-BuLi in THF at −90 °C in the presence of 6 equiv of HMPA for 30 min), and the reaction mixture was then stirred for 1 h at −30 °C to establish the thermodynamic equilibrium prior to quenching with 2,6-di-*tert*-butyl-4-methylphenol[13] at −90 °C (Scheme 5). Under these conditions, compounds **4** and **13** were obtained in a ratio of 55:45 in 88% yield (Table S2, Supporting Information). The separation of both isomers by flash column chromatography allowed the spectroscopic characterization of **13** (see Supporting Information). One-dimensional gNOESY experiments confirmed the structural assignment previously made: the selective excitation of the ortho protons of the *P*-phenyl ring ($H_P°$) and of H3a produced NOEs on H3 and the ortho protons of the phenyl ring (H°) linked to C3, respectively (Figure S10, Supporting Information).

Conclusions

A detailed picture of the lithiation of *N*-methyl-*N*-benzyldiphenylphosphinamides (**1**) with *s*-BuLi in THF has been obtained by deuterium labeling and multinuclear magnetic resonance studies. In the absence of coordinating cosolvents such as HMPA or DMPU, the lithiation of **1** and subsequent trapping reaction with D_2O revealed that the phosphinamide group is capable of directing the metalation to the ortho and benzylic positions, with a preference for the latter by a factor of almost 2. Ortho-to-benzylic anion translocation occurs only when HMPA or DMPU is present in the reaction medium, as evidenced by the scrambling of deuterium in the anionic dearomatization of a derivative of **1** dideuterated at the benzylic position. NMR monitoring of the reaction allowed us to unravel the detailed reaction pathway. First, in the absence of HMPA, two diastereomeric *s*-BuLi-phosphinamide precomplexes, **Va** and **Vb**, are formed. These are dimeric precursors for the deprotonation at the benzylic position (CIPE mechanism). Moreover, for the **Vb** dimer a slow inversion at the carbanion center of the *sec*-butyllithium was observed. The benzylic anion **II** is a monomer of relatively short half-life (<90 min) evolving through intramolecular attack of the carbanion center at each of the diastereotopic *P*-phenyl rings. As a result, the four monomeric dearomatized anions **III**, **IV**, **VI**, and **VII** (initial ratio of 1:0.07:0.13:0.25) are obtained. These four anionic species are in equilibrium (i.e., the anionic cyclization is a reversible process). On the other hand, a significant amount of ortho deprotonation leading to **I** takes place in the initial moments of the reaction. The ortho anion **I** is assumed to be a dimer of undefined structure arising from two highly reactive precomplexes **VIIIa** and **VIIIb** (CIPE mechanism), isomers of **Va** and **Vb**, that could not be detected. They do not equilibrate with **Va** and **Vb** under the conditions used. Once formed, **VIIIa** and **VIIIb** immediately progress to the ortho anion **I,** whose concentration remains constant from that instant. When the reaction reaches a steady state, only anions **I**, **III**, and **IV** are observed in solution (relative ratio of 1.2:1:0.1). The dearomatized anions **III** and **IV** represent the precursors of the products of kinetic and thermodynamic control, respectively. The deprotonation of **1** in the presence of HMPA directly gives a mixture of **III** and **IV** in a ratio of 1:0.6. In this case the lithium atom is coordinated to one molecule of HMPA. Thus, the cosolvent catalyzes the translocation of the ortho anions **I** to the benzylic species **II** as well as the dearomatizing cyclization reaction. One-dimensional $^{7}Li\{^{31}P,^{1}H\}$ and 2D $^{7}Li,^{31}P\{^{1}H\}$ HMQC NMR experiments proved to be excellent tools for the structural assignment of lithiated organophosphorus compounds containing a P═O group. The fact that anion **IV** predominates at temperatures above −30 °C is synthetically meaningful because it gives access to a new family of dearomatized compounds with a different configuration at the phosphorus center with respect to those usually isolated in the anionic dearomatizing−electrophilic alkylation reactions of phosphinamides.

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Supporting Information Available: Experimental details including NMR sample preparation, relevant spectrometer information, synthetic procedures, and characterization of **1-*d*$_2$**, **7-*d*$_2$**, **8-*d*$_2$**, **9-*d*$_2$**, **4**, and **13**. 2D $^{1}H,^{31}P$ gHMQC, $^{1}H,^{13}C$-gHMQC, and $^{1}H,^{13}C$-gHMBC NMR spectra of the lithiation of **1** at −90 °C in THF-d_8. Evolution of ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra of the lithiation of **1** as a function of metalation time (t_1). $^{31}P\{^{1}H\}$ NMR spectrum at $t_1 = 2$ min of lithiation at −90 °C in THF-d_8 with and without resolution enhancement (LB = 2). 2D gROESY spectrum of the lithiation of **1** in the presence of

HMPA. $^{31}P\{^{1}H\}$, $^{7}Li\{^{1}H\}$, and $^{7}Li\{^{31}P,^{1}H\}$ NMR spectra of the lithiation of **1** at −110 °C in the presence of HMPA. Temperature effect on the olefinic region of the ^{1}H and $^{1}H\{^{31}P\}$ NMR spectra of the mixture **I**, **III,** and **IV** in the absence of HMPA. 1D gNOESY rows corresponding to the selective excitation of **13**. Product distribution in the dearomatization−protonation reaction of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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