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Mechanism of Anionic Dearomatizing Reactions of Diphenylphosphinamide Derivatives: A Theoretical and Experimental Study

Antonio Morán Ramallal,[b] Ignacio Fernández,[a] Fernando López Ortiz,*[a] and Javier González*[b]

Abstract: The mechanism of the anionic dearomatisation of phosphinamide derivatives has been investigated both theoretically and experimentally. The potential-energy surface of model reactions was studied at the Becke3LYP/6-31+G* level of theory, and according to this study, a pre-reactive complex is formed between the alkyllithium and the phosphinamide. This complex evolves preferentially through NC_{α}-metalation of the phosphinamide. The intramolecular nucleophilic addition of the carbanion to the *ortho* position of the aromatic ring leads to the dearomatised products, in a reaction that has been shown to be under thermodynamic control. Coordinating co-solvents, such as hexamethyl phosphoramide (HMPA) or *N*,*N*′-dimethyl-*N*,*N*′-propylene urea (DMPU), appear to influence the reaction by favouring the formation of solvent-separated ion pairs. The cyclisation reaction of allylphosphinamide derivatives was also studied. It was found that both the α- and γ-attack of the allyl anion can take place, however the formation of the seven-membered ring products derived from the γ-attack are clearly favoured.

Keywords: anions · dearomatization · density functional calculations · lithiation · phosphinamides · solvent effects

Introduction

The addition of main-group organometallic reagents to aromatic compounds is an efficient method for breaking down the conjugate π system of an aromatic ring and has been extensively used for the preparation of functionalised alicyclic and acyclic compounds.[1] In arenes these dearomatising reactions are generally limited to polycyclic systems.[2] On the other hand, conjugate addition to aromatic hydrocarbons bearing electron-withdrawing groups (e.g., aldehyde and ketone,[3] imines,[4] carboxylic acid,[5] carboxylic ester,[6] carboxamides,[7] acyl halide,[8] nitriles,[9] oxazolidines,[10] oxazolines,[11] triazenes[12]) has much wider scope as revealed by the application of this methodology to the synthesis of several natural products[13] and non-natural analogues.[14] In *N*-benzylcarboxamides,[15] phenyl sulfones,[16] *N*-benzylsulfonamides[17] and *N*-benzyldiphenylphosphinamides,[18] the dearomatisation may take place intramolecularly through an anionic cyclisation reaction.

We have recently shown in a synthetic[19] and NMR[20] study that upon treatment of *N*-benzyl-*N*-methyldiphenylphosphinamide **1a** (Scheme 1) with *sec*-butyllithium in tetrahydrofuran (THF) at −90 °C the mechanism of the cyclodearomatising reaction involves the formation of a dimeric precomplex **I** between the starting phosphinamide and the base, which evolves by *ortho*-directed and benzylic lithiation to give the lithium intermediates **II** and **III**, respectively. The benzylic anion **III** undergoes a cyclisation through intramolecular attack at the *ortho* position of a P-substituted phenyl ring leading to the four possible dearomatised diastereoisomers **IV**–**VII**. The reaction progresses to yield an equilibrium mixture of derivatives **IV** and **V**, plus the *ortho*-lithiated intermediate **II**. Compounds **III** to **VII** have been identified as monomeric, whereas **II** has been assigned as di-

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains Cartesian coordinates and energies of the stationary points located, $^{31}P\{^1H\}$ NMR spectra showing the product distribution in the dearomatisation–protonation reaction of **1b** and 1D gTOCSY NMR spectra of compounds **3a** and **3b**.

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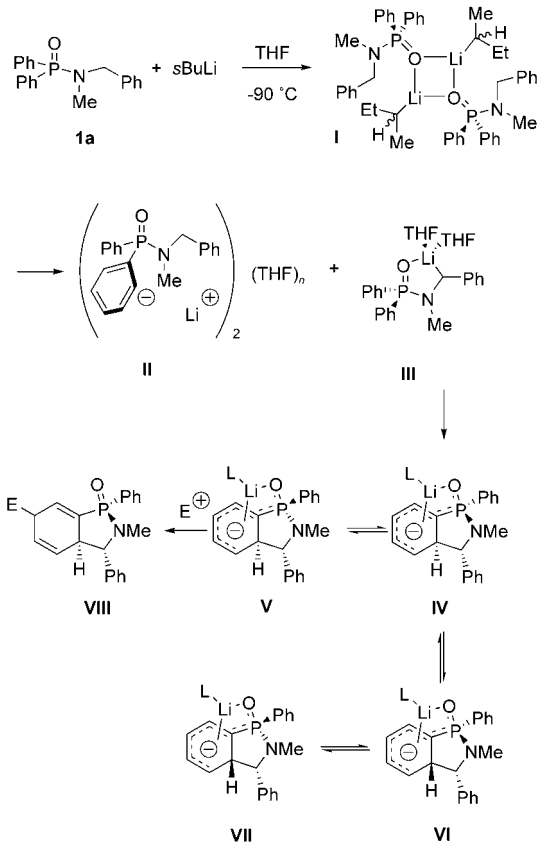


Scheme 1. Metalation and cyclisation reactions of phosphinamide **1a** (L = THF or HMPA).

Abstract in Spanish: *Se ha investigado, teórica y experimentalmente, el mecanismo de la reacción de desaromatización aniónica de derivados de fosfinamidas. La superficie de energía potencial de reacciones modelo se estudió al nivel de teoría Becke3LYP/6-31+G*. De acuerdo con este estudio, se encontró que el proceso se inicia con la formación de un complejo pre-reactivo entre el alquil litio y la fosfinamida, a partir del cual se produce la metalación en la posición NC_α- preferentemente respecto a la litiación en posición* orto*. La adición intramolecular del carbanión a la posición* orto *del anillo aromático conduce a los productos de desaromatización, en una reacción que está regida por control termodinámico. Los disolventes coordinantes como la HMPA o la DMPU parecen influir en la reacción favoreciendo la formación de pares iónicos separados por el disolvente. Se estudió también la reacción de ciclación de derivados de allilfosfinamida, encontrándose que la ciclación aniónica puede tener lugar tanto por el ataque a través depor las posicióones α como de la γ del anión alilo. No obstante, la formación de los productos con estructura cíclica de siete eslabones, procedentes del ataque por la posición γ está claramente favorecida.*

meric. In the presence of hexamethyl phosphoramide (HMPA) or *N*,*N*′-dimethyl-*N*,*N*′-propylene urea (DMPU), translocation of the *ortho* anion **II** to the benzylic anion **III** takes place and the only lithium compounds observed in solution are the dearomatised anions **IV** and **V**.

In sharp contrast, the lithiation of **1a** with *tert*-butyllithium in diethyl ether at −90 °C leads exclusively to the formation of benzylic anions as a mixture of monomeric and dimeric species.[21]

Although the solution NMR study allowed us to identify the reaction intermediates involved in the transformation of phosphinamide **1a** into the tetrahydrobenzophosphole derivatives **VIII**, some aspects of the mechanism still require clarification. Calculation of the energy profile of the process would be of great interest for understanding some details of the reaction pathway given in Scheme 1, such as the distribution of *ortho* and benzylic anions obtained when the metalation is carried out in the absence of coordinating solvents, the translocation mechanism and the stereochemical preferences of the anionic cyclisation reaction. In addition, the accelerating effect of HMPA and DMPU is poorly understood.

Ortho-directed metalation of an aromatic ring[22] and benzylic lithiation[22g,23] reactions have been the subject of several theoretical studies. Bailey et al. also investigated theoretically the anionic cyclisation involving an isolated carbon–carbon double bond on 2-(2-vinylphenyl)propyllithium.[24] In a recent communication we have shown that the anionic cyclodearomatisation of phosphinamides can be described as a Michael-type ionic process[25] in contrast to the electrocyclic ring closure suggested for the analogous reaction of lithiated *N*-benzylarylamides.[26] However, to the best of our knowledge, the theoretical grounds of the dearomatising anionic cyclisation have not been previously explored.

In order to get a deeper insight into the mechanism of the anionic dearomatisation of phosphinamides, we performed a study of the potential-energy surface of several model systems based on the four steps experimentally observed: 1) precomplexation, 2) competing *ortho*-directed aromatic metalation and NC_α-metalation, 3) anion translocation and 4) intramolecular cyclisation. The influence of solvents on the reaction course was also analysed. In addition, the different cyclisation modes of *N*-alkyl-*N*-allyldiphenylphosphinamide (**1b**) to give the five- or seven-membered systems, **2** and **3** (see Figure 1), respectively, were investigated both theoretically and experimentally.

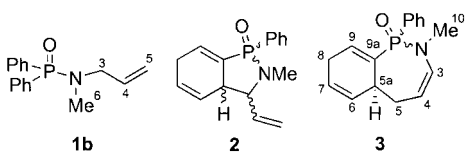


Figure 1. *N*-Allylphosphinamide **1b** and five- and seven-membered ring cyclisation products **2** and **3**.

Results and Discussion

Computational methods: As a result of the size of the systems being studied, density functional theory (DFT) methods were employed because they offer a reasonable balance between the reliability of the calculation and the computational cost.[27]

The geometry of each stationary point was fully optimised at the Becke3LYP/6-31+G* or Becke3LYP/3-21+G* level of theory, and the nature of all the stationary points located was verified by frequency calculations. All calculations were carried out with the Gaussian 98 suite of programs.[28]

Potential-energy surface for the lithiation step: To use the simplest model for studying the two possible competing reaction pathways for the metalation, we considered the reaction of model phosphinamide **1c** with methyllithium (as a model of the lithiation reagent) to give the metalated intermediates **4** or **5** (see Figure 2). The organolithium compounds were considered to be monomers.

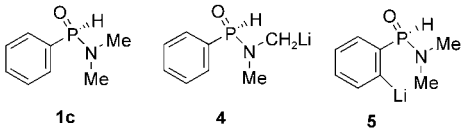


Figure 2. Model phosphinamide **1c** and C_α- and *ortho*-metalated intermediates **4** and **5**, respectively.

The stationary points located for the *ortho*- and α-directed lithiation reactions of **1c** are shown in Figure 3, and their relative energies are listed in Table 1.

According to our results, both reactions start with the barrierless formation of complexes **6** and **8**, between the phosphinamide and MeLi, which are strongly stabilised with respect to the reagents. The formation of very stable complexes between organolithium reagents and substituted benzenes has been widely documented, and its role on the aromatic lithiation reaction has been studied.[29,30] *Ortho*-directed deprotonations have alternatively been described as kinetically controlled transformations.[22b–e] In the pre-reactive complexes **6** and **8**, the methyllithium reagent is coordinated to the P=O bond of the phosphinamide moiety, as indicated by the increase of the P=O bond length from 1.502 Å in phosphinamide **1c** to 1.522 Å or 1.517 Å in structures **6** and **8**, respectively. The two pre-reactive complexes show a similar stability and differ only in the relative orientation of the MeLi fragment with respect to the aromatic ring: In complex **6**, which leads to the α-lithiated intermediate, the Me and NMe_2 fragments show a relative *syn* orientation, while in **8**, the methyl fragment is close to the *ortho* hydrogen in the phenyl ring.

Next in the reaction coordinate two transition structures, **7** and **9**, were located. In **7**, the C_α–Li bond is being formed as

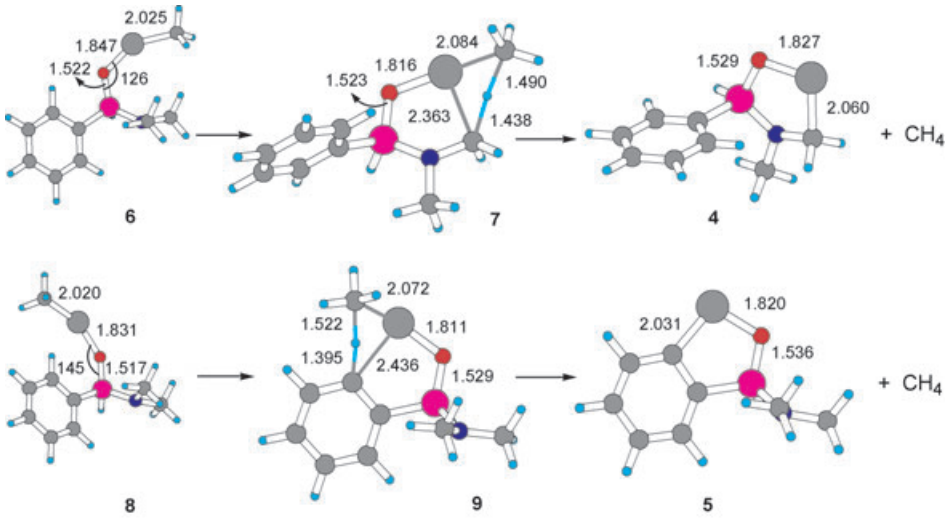


Figure 3. Stationary points found for the lithiation reaction of model phosphinamide **1c**. Bond lengths in Å and angles in degrees. Colour code of spheres: light blue = hydrogen, small grey = carbon, large grey = lithium, red = oxygen, dark blue = nitrogen, pink = phosphorus.

Table 1. Relative energies [kcal mol^{-1}] of the stationary points located for the metalation and translocation reactions.

Reaction	Stationary point	Relative energy[a]
α-directed lithiation of **1c**	**6**	−28.3
	7	−1.3
	4+CH_4	−28.2
ortho-directed lithiation of **1c**	**8**	−27.9
	9	−8.1
	5+CH_4	−37.6
ortho-directed lithiation of **10**	**12**	27.9
	14	−8.2
	16a+CH_4	−37.7
α-directed lithiation of **10**	**13**	−28.2
	15	−9.9
	16b+CH_4	−41.7
α-directed lithiation of **11**	**17**	−28.6
	18	−10.4
	19+CH_4	−40.6
anion translocation of **5**	**5**	0.0[b]
	20	+41.2
	4	+9.3

[a] The relative energies refer to the sum of the energies of neutral phosphinamides and methyllithium. [b] In this reaction, the energies are calculated with respect to the *ortho*-lithiated intermediate.

the C_α–H bond elongates, leading to the formation of a methane molecule and the α-lithiated intermediate **4**. Similarly, in the transition structure **9**, the simultaneous abstraction of the *ortho* hydrogen and the formation of the C_{ortho}–Li bond takes place. The bond between the hydrogen being abstracted and the carbon atom is almost completely broken in the transition structures, as can be seen from the values of the corresponding bond lengths: 1.438 (C_α–H in **7**) and 1.395 Å (C_{ortho}–H in **9**). Also, in both transition structures the lithium atom remains bonded to the oxygen atom, so in intermediates **4** and **5** lithium is di-coordinated.

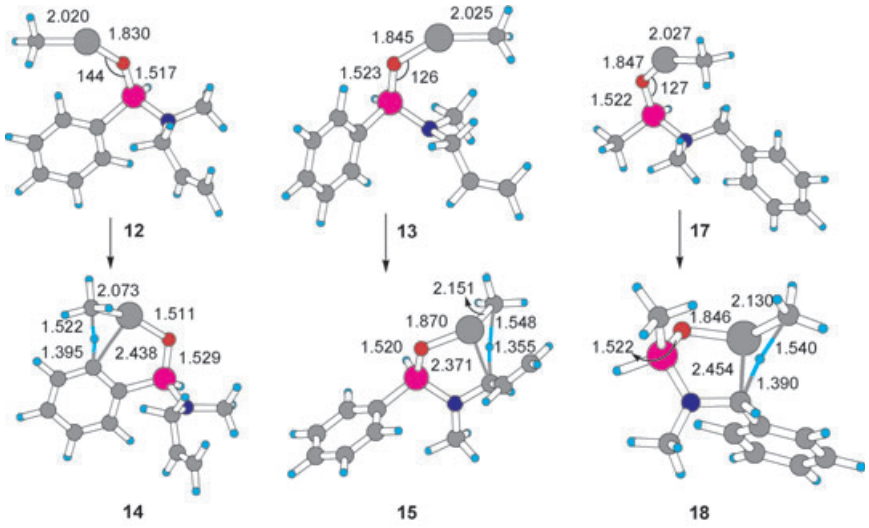


Figure 5. Pre-reactive complexes **12**, **13** and **17**, and transition structures **14**, **15** and **18** located for the lithiation of model *N*-allyl- and *N*-benzyl phosphinamides **10** and **11**, respectively. Bond lengths in Å and angles in degrees. For the colour code see the legend of Figure 3.

From the values of the relative energies (Table 1), the metalation of model phosphinamide **1c** is predicted to take place at the *ortho* position of the phenyl ring, as could be expected from the corresponding pK_a values of the aromatic and aliphatic hydrogen atoms. However, the experimental results indicate that the cyclodearomatising reaction of phosphinamides requires always the presence of one benzyl or allyl group (see below) on the phosphinamide nitrogen (see Figure 1). In order to test the influence of these substituents on the metalation site, we investigated the *ortho*- and α-directed metalation pathways of the model phosphinamides **10** and **11**, shown in Figure 4. In the case of the benzylic metalation, the small model phosphinamide **11** was used, due to computational limitations.

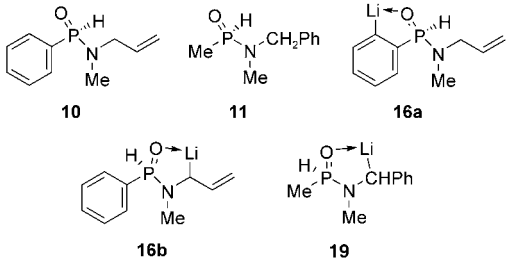


Figure 4. *N*-Allyl- (**10**) and *N*-benzyl- (**11**) model phosphinamides and lithiated derivatives **16a**, **b** and **19**.

The potential-energy surface for the lithiation reaction of phosphinamides **10** and **11** is qualitatively similar to the one found for the phosphinamide **1c** (see Figure 5 and Table 1).

The pre-reactive complexes initially formed (**12**, **13** and **17**) are followed by the transition structures corresponding to the *ortho*, allylic and benzylic metalation reactions (**14**, **15** and **18**, respectively). However, while the barrier for the *ortho*-directed lithiation is almost the same for **1c** and **10** (see data in Table 1), the barrier for the α-directed lithiation is drastically reduced in the case of the *N*-allylphosphinamide **10** and now the metalation takes place at the allylic position, the C_α-lithiated intermediate **16b** being predicted to be both the kinetic and thermodynamic product. The results of **11** are similar to the allylic derivative **10** (Figure 5 and Table 1): a small barrier was found for the metalation of the C_α-position.

Anion translocation step: According to the previous results, the metalation of the phosphinamides bearing carbanion-stabilizing groups (e.g., benzyl or allyl) at the nitrogen is expected to take place at the α-carbon atom. In work closely related to this, Clayden and co-workers proposed that upon treatment of *N*-alkyl-*N*-benzylarylcarboxamides with a lithium base the metalation could initially occur to some extent at the *ortho* position of the aromatic ring, and then a translocation of the negative charge would lead to the NC_α-lithiated anion.[31]

The translocation reaction was studied for the case of phosphinamide **3**, and the transition structure **20** (Figure 6), corresponding to the transformation of the *ortho*-lithiated phosphinamide **5** into the α-anion **4**, was located.

In transition structure **20**, one of the hydrogen atoms of the methyl group is being transferred to the *ortho* position in the aromatic ring, while the lithium atom remains simultaneously bonded to the oxygen and to the aromatic and aliphatic carbon atoms. However, this translocation step has a high activation barrier (see Table 1), so this reaction pathway can be excluded as being responsible for the formation of the α-lithiated intermediates in the cyclodearomatisation of phosphinamides. This result is in agreement with the experimental observation that *ortho*-lithiated compound **1a**

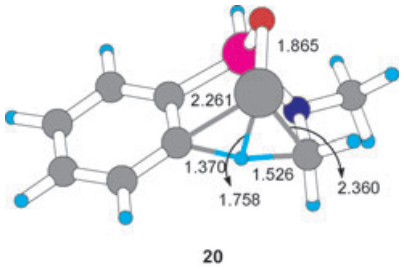
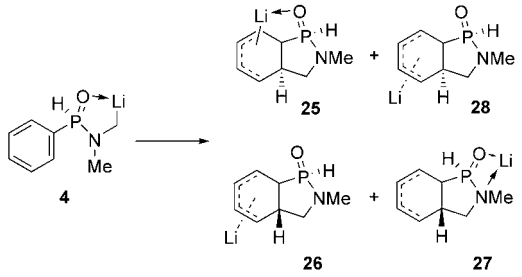


Figure 6. Transition structure **20** for the anion translocation. Bond lengths in Å. For the colour code see the legend of Figure 3.

does not evolve into dearomatised products in the absence of HMPA or DMPU at −90 °C.[19,20]

Potential-energy surface for the cyclisation step: According to the previously described results, the lithiation of benzyl or allyl phosphinamides will lead to a benzylic or allylic organolithium, which will undergo intramolecular cyclisation by nucleophilic attack of the carbanionic centre at the *ortho* position of the aromatic ring. As can be seen in Scheme 2,



Scheme 2. Stereoisomeric products in the cyclisation reaction of **4**.

four different stereoisomers could be formed in the cyclisation reaction of the α-metalated intermediate **4**, depending on the face (*re* or *si*) of the aromatic ring undergoing the addition and the relative orientation of the lithium atom with respect to the phosphorous–oxygen bond.

The geometries and activation and reaction energies of the transition structures (**21**–**24**) are shown in Figure 7. In the transition structures, the lithium atom is bonded either to the oxygen and nitrogen atoms, as in **23**, or to the aromatic ring in a η^6 fashion, as in **21**, **22** and **24**, and the vibrational normal mode associated with the imaginary frequency corresponds to the stretching of the C–C forming bond.

According to the characteristics of these transition structures, the cyclisation reaction of lithium phosphinamide **4** can be considered as a Michael-type ionic nucleophilic addition and not an electrocyclic reaction.[25]

From the energetic data shown in Figure 7, it can be seen that transition structures **23** and **21**, for the cyclisation involving the *re* and *si* faces of the aromatic ring, respectively, differ only in 0.8 kcal mol^{-1}, while the stability of the corresponding products, **27** and **25**, is quite different in that **25** is predicted to be the most stable by 11.5 kcal mol^{-1}. Following these data, **27** and **25** can be considered as the products of kinetic and thermodynamic control, respectively. As the barrier for the reversion of the kinetic control isomer **27** is 12.3 kcal mol^{-1} lower than the reversion barrier for the thermodynamic control isomer **25**, it could be proposed that under thermodynamic-control conditions in the cyclodearomatising reactions of phosphinamides the major product will be that corresponding to the *si* cyclisation mode, **25**, in good agreement with the experimental results.[19] Despite this agreement, it is important to note that the predicted activation-barrier results are quite high for reactions that take place at very low temperatures. This could be an indication of the limitations of the previous model, as the solvent effects were not taken into account.

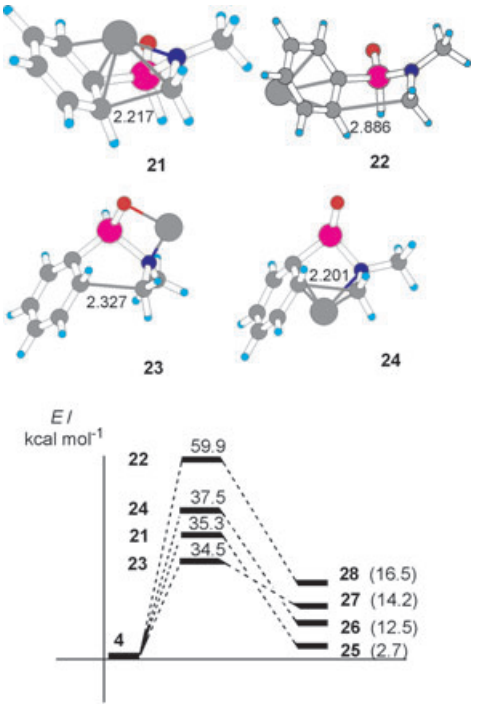
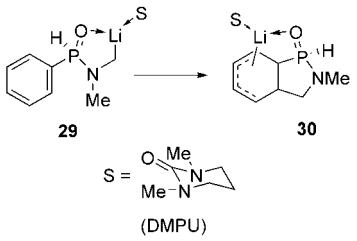


Figure 7. Transition structures, activation barriers and reaction energies for the cyclisation reaction of anion **4**. Bond lengths in Å. For the colour code see the legend of Figure 3.

Solvent effects: According to the experimental evidence, coordinating solvents such as HMPA and DMPU strongly influence the course of the cyclodearomatising reactions, because in the absence of a co-solvent, the reaction takes place very slowly.[19,21] The effect of these co-solvents can be attributed to their ability for coordinating the lithium cation. In order to evaluate the solvent effect we studied the potential-energy surface for the model reaction shown in Scheme 3, corresponding to the cyclisation of the DMPU-solvated anion **29**. In this case, the lithium atom in each stationary point is coordinated to one molecule of DMPU. Due to the size of the system, the stationary points were optimised at the Becke3LYP/3-21+G* level of theory; for com-



Scheme 3. Model reaction for the cyclisation of DMPU-coordinated anion **29**.

parison with the results obtained on the unsolvated model, the corresponding stationary points (**4**, **21** and **25**) were also re-optimised at the same level of theory.

The DMPU-coordinated transition structure for the cyclisation reaction of **31** and the relative energies of the two reaction pathways are shown in Figure 8. It can be seen that in

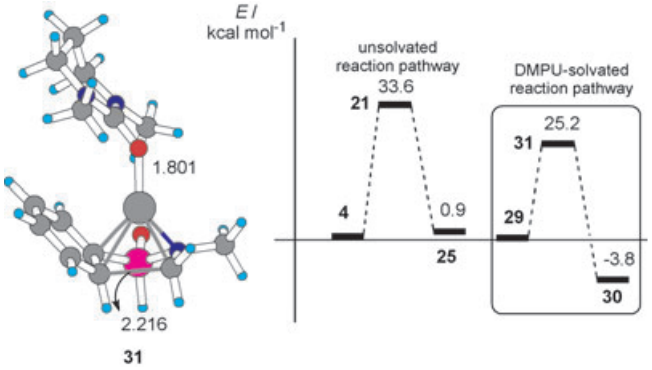
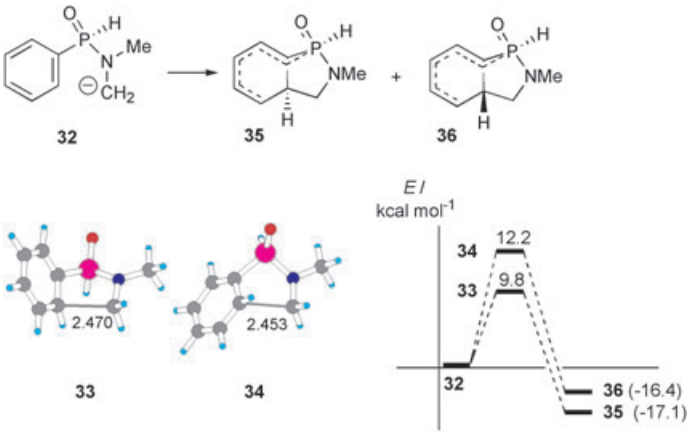


Figure 8. Becke3LYP/3-21+G* optimised DMPU-solvated transition structure and reaction profiles for the solvated and unsolvated cyclisation reactions. Bond lengths in Å. For the colour code see the legend of Figure 3.

transition structure **31**, corresponding to the *si*-face cyclisation, the DMPU molecule is coordinated to the lithium atom, which is still bonded to the organic fragment. The basic geometric features of this transition structure are very close to those found for the reaction without a solvent molecule, but the presence of the DMPU molecule significantly alters the reaction profile: the activation barrier for the cyclisation is reduced by 8.4 kcal mol^{-1} and the stability of the reaction product increases, product **30** being predicted to be 3.8 kcal mol^{-1} more stable than the starting anion **29**.

This result shows that the critical role played by strongly coordinating co-solvents such as HMPA or DMPU in the cyclodearomatising reaction of lithium phosphinamides may be related to the reduction of the activation barrier upon complexation of the lithium atom with the strongly coordinating additive. This proposal is in good agreement with the results reported by Reich and co-workers in the study of the effect of polar coordinating additives (such as HMPA) on the structure of different types of organolithium compounds.[32] According to these results, the ion-pair structure of organolithium reagents in the presence of strongly coordinating ligands will change from a contact ion pair to a solvent-separated ion pair thus making the interaction between the lithium atom and the organic fragment of the organolithium compound weaker and increasing the anionic reactivity of the counterion.

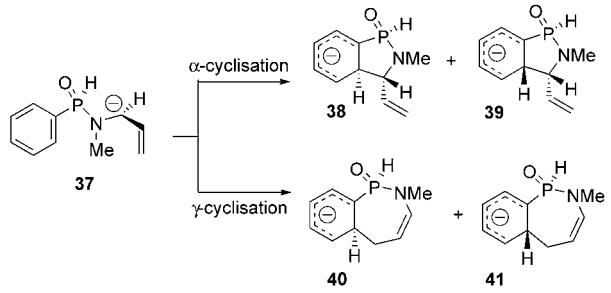
In order to test this hypothesis in the case of the anionic cyclodearomatisation of lithium phosphinamides, additional calculations were carried out by using an anionic system to model the conditions corresponding to a solvent-separated ion pair. Thus, the potential-energy surface for the cyclisation reaction of anion **32** was studied and two transition structures, **33** and **34**, were located (Scheme 4).



Scheme 4. Transition structures and reaction profile for the cyclisation of the anion **32**. For the colour code see the legend of Figure 3. Bond lengths in Å.

The cyclisation of anion **32** takes place through the stereoisomeric transition structures **33** and **34**, which show a geometry closely resembling one of the transition structures found in the neutral system (see Figure 7), but with the C–C forming bond being less formed than in the case of **21** and **23**, indicating an earlier transition structure. However, the potential-energy surface for the cyclisation of anion **32** is different from that corresponding to the α-metalated phosphinamide **4**. It is interesting to note that the activation barrier for the cyclodearomatisation reaction of **32** is predicted to be notably lower than the values found for **4**. This result seems to indicate that the increase of the anionic character of the species involved in the reaction, for example, by the effect of the coordinating additives, will cause a significant reduction of the reaction barrier, in good agreement with the experimental findings.

Anionic cyclodearomatisation of *N*-allylphosphinamide (10): The model reaction shown in Scheme 2 does not allow for a detailed discussion of the stereochemistry of the cyclisation reaction due to the lack of substituents on the carbon atom at the α-position relative to the nitrogen atom. As a more suitable model, according to the previous discussion, we studied the cyclodearomatising reaction of anion **37** (Scheme 5), derived from *N*-allylphosphinamide **10** (Figure 4).



Scheme 5. Cyclisation reaction of allylic anion **37**.

In this case, due to the presence of the allyl group, the cyclisation reaction can occur either at the α-position, to give the five-membered products, **38** and **39**, or at the γ-carbon atom, giving the seven-membered bicyclic systems **40** and **41**. In the case of the five-membered products, four possible stereoisomers may be formed from **38** and **39**.

Two transition structures (**42** and **43**, Figure 9) were located for the α-cyclisation of allyl anion **10**, leading to the *trans* and *cis* products **38** and **39**, respectively. The geometry and relative energies of the transition structures corresponding to the cyclisation at the α-position of the allyl anion are very similar to those found for anion **32** (Scheme 4). In this case, the *trans* product **38** is predicted to be formed preferentially in the α-cyclisation reaction, in good agreement with the experimental evidence indicating that the C–C bond formation in the anionic cyclodearomatisation is stereoselective, the *trans* isomer being the major product.

On the other hand, according to the energetic data shown in Figure 9, the cyclodearomatisation of **37** is predicted to give the seven-membered ring derivatives **40** and **41** as major products, corresponding to the γ-cyclisation of the allyl anion via transition structures **44** and **45**. In this case, **41** is predicted to be the kinetic product, and **40** the thermodynamic one.

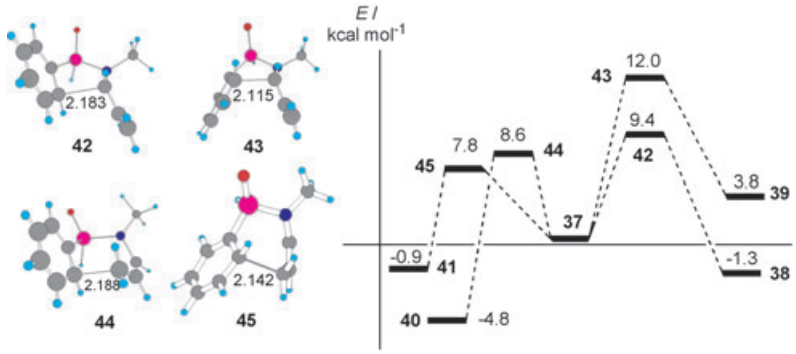
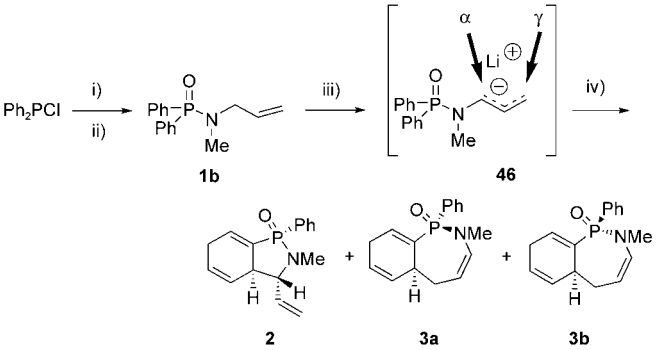


Figure 9. Becke3LYP/6-31+G* transition structures and relative energies for the α- and γ-cyclisation reactions of *N*-allylphosphinamide anion, **10**. Bond lengths in Å.

Experimental study of the anionic cyclodearomatisation of *N*-allylphosphinamide (1b): In order to check the validity of the prediction regarding the favoured formation of a seven- as opposed to a five-membered ring in the anionic cyclisation of allylphosphinamides, we prepared phosphinamide **1b** (Figure 1) following the procedure previously reported for the synthesis of **1a** and outlined in Scheme 6.[18b]



Scheme 6. Synthesis of *N*-allylphosphinamide **1b** and subsequent dearomatising reaction: i) $MeNHCH_2CH{=}CH_2$, NEt_3 (2.5 equiv), toluene, −78 °C; ii) H_2O_2 (1 equiv), −30 °C, THF; iii) RLi (2.5 equiv), DMPU (6 equiv), THF, −90 °C, t_1; iv) 2,6-di-*tert*-butyl-4-methylphenol (5 equiv), −90 °C, 30 min.

The dearomatisation of **1b** and subsequent protonation with 2,6-di-*tert*-butyl-4-methylphenol under the same conditions described for the analogous reaction of phosphinamide **1a** (metalation: *s*BuLi (2.5 equiv), THF, −90 °C in the presence of DMPU (6 equiv) for 30 min; protonation: 30 min, −90 °C) resulted in the formation of a mixture of compounds **2**, **3a** and **3b** (Scheme 6) in a ratio of 10:53:37, respectively, and in a 62 % yield (Table 2, entry 1).

Table 2. Distribution of products in the dearomatisation–protonation of **1b**.

RLi	t_1 [h]	Ratio **3a**	**3b**	**2**	Yield [%]	**1b** [%]
*s*BuLi	0.5	53	37	10	62[a]	12
*s*BuLi	12	57	34	9	84[a]	7
*t*BuLi	24	60	32	8	98	–

[a] Recovered $Ph_2P(O)$-*s*Bu (9 %).

In agreement with the previous theoretical calculations, the formation of the seven-membered rings, **3a** and **3b**, by γ-attack of the allylic anion **46** to one P-substituted phenyl ring is largely favoured as compared with the anionic cyclisation derived from the α-attack (ratio of γ-/α-attack of 90:10). In this case, two stereoisomers were formed as two phenyl rings can experience the nucleophilic attack of the γ-carbanionic centre.

The recovery of 12% of **1b** suggests that the metalation time (t_1) was too short. This hypothesis was confirmed by the 84% yield obtained when t_1 was increased to 12 h (Table 2, entry 2). However, in both cases 9% of the starting phosphinamide was transformed into the phosphine oxide $Ph_2P(O)$-*s*Bu by attack of the base on the phosphorus atom of **1b**. This competing reaction was completely inhibited by using bulky *t*BuLi as the base. Additionally, the metalation was allowed to take place for 24 h to assure the complete conversion of **1b** (see Supporting Information). Under these conditions, **1b** gave a mixture of **3a**/**3b**/**2** in a ratio of 60:32:8 almost quantitatively (Table 2, entry 3).

Flash column chromatography of the crude reaction mixture afforded mixtures enriched in **3a** and **3b** (see Experimental Section) which allowed us to identify each product based on the analysis of their NMR spectra. The small amount of azaphosphole **2** present could not be isolated. The pattern of the signals observed for this compound in the proton spectrum of the crude reaction mixture and the selective experiments performed (1D gTOCSY, 1D gNOESY) allowed the identification of its structure. Focusing on **3a**, the [1,4] dienic system of the dearomatised ring is characterised by the large deshielding and coupling to the phosphorus nucleus shown by the proton at the β-position relative to the P–O linkage ($\delta = 7.19$ ppm, $^3J_{PH} = 20.6$ Hz).[18b] The γ-attack of the allylic anion leading to formation of the seven-membered ring is shown in the ^{13}C NMR spectrum by the appearance of a methylene signal at $\delta = 32.97$ ppm and two enamine carbons at $\delta = 113.15$ ($^3J_{PC} = 3.6$ Hz) and 134.521 ppm ($^2J_{PC} = 1.6$ Hz) corresponding to the $CH_2CH{=}CHN$ fragment. The correlations observed in the 2D gHMQC and HMBC spectra confirmed the assignments. The relative configuration of the stereogenic centres was assigned through a 2D gNOESY experiment. The *syn* arrangement of the bridgehead proton and the P-substituted phenyl substituent was deduced from the correlation observed between that methine proton and the *ortho* protons of the P-substituted phenyl ring.

Conclusion

According to the density theory calculations reported, the anionic cyclodearomatising reaction of phosphinamides is predicted to occur by a two-step mechanism, involving the metalation at the benzylic or allylic position and the intramolecular, nucleophilic attack of the anionic centre at the *ortho* position of the aromatic ring. The formation of the dearomatised cyclic products is subjected to thermodynamic control, and the critical role played by the coordinating additives seems to be a result of the solvent-separated ion pair character of the organolithium intermediates involved. The cyclisation of allylphosphinamide derivatives was shown to occur preferentially at the γ-position of the allyl moiety, in good agreement with the theoretical calculations.

Experimental Section

General methods: All reactions and manipulations were carried out in a dry, N_2-gas atmosphere using standard procedures. THF was distilled from sodium/benzophenone immediately prior to use. DMPU was distilled from CaH_2 under reduced pressure. Commercial reagents were purchased from Sigma-Aldrich Química, S.A., and were all distilled prior to use except for *s*BuLi. Thin-layer chromatography (TLC) was performed on Merck plates with aluminium backing and silica gel 60 F_{254}: For column chromatography silica gel 60 (40–63 μm) from Scharlau was used. Mass spectra were determined by atmospheric pressure ionization electrospray (API-ES) on a Hewlett–Packard 5987 A or 1100 apparatus. NMR spectra were recorded on a Bruker Avance DPX300 using $CDCl_3$ as solvent. Chemical shifts are referenced to internal tetramethylsilane for ^1H (300.13 MHz) and ^{13}C (75.47 MHz), and to external 85% H_3PO_4 for ^{31}P (121.47 MHz). 2D NMR correlation spectra (gCOSY, gTOCSY, gNOESY, gHMQC and gHMBC) and selective 1D gTOCSY and gNOESY were acquired by using standard Bruker software and processing routines.

***N*-Allyl-*N*-methyldiphenylphosphinamide (1b)**: *N*-Allyl-*N*-benzylamine (2 mL, 15.03 mmol) was added to a solution of chlorodiphenylphosphine (2.69 mL, 15.03 mmol) and triethylamine (5.21 mL, 37.6 mmol) in toluene (100 mL) at −78 °C. The mixture was stirred for 30 min and then H_2O_2 (30% v/v; 1.7 mL, 15.03 mmol) was added. Oxidation was completed in 1 h, and then the reaction was poured into ice water and extracted with ethyl acetate (3×15 mL) and washed with 0.1 N NaOH (2×15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo affording **1b** as a pale yellow oil. The purity of the phosphinamide was higher than 97% (NMR) and was used without further purification. Yield: 90–95%; oil; ^1H NMR: $\delta = 2.61$ (d, $J_{PH} = 10.8$ Hz, 3H; H-6), 3.54 (dd, $J_{PH} = 7.3$, $J = 6.2$ Hz, 2H; H-3), 5.21 (dd, $J = 10.3$, $^2J_{HH} = 2.9$ Hz, 1H; H-5), 5.23 (ddd, $J = 17.2$, $J = 2.9$, $J = 1.4$ Hz, 1H; H-5′), 5.80 (ddt, $J = 17.2$, $J = 10.3$, $J = 6.2$ Hz, 1H; H-4), 7.56–7.41 (m, 6H), 7.88 ppm (m, 4H); ^{13}C NMR: $\delta = 33.54$ (d, $J_{PC} = 3.0$ Hz; CH_3), 51.94 (d, $J_{PC} = 3.0$ Hz; CH_2), 117.73 ($H_2C{=}$), 128.51 (d, $J_{PC} = 12.6$ Hz; CAr), 131.71 (d, $J_{PC} = 3.0$ Hz; CAr), 131.78 (d, $J_{PC} = 129.2$ Hz; C_{ipso}), 132.26 (d, $J_{PC} = 9.0$ Hz; CAr), 134.40 ppm (d, $J_{PC} = 6.6$ Hz; HC=); ^{31}P NMR: $\delta = 31.47$; MS (API-ES): *m*/*z* (%): 295 $[M+H+Na]^+$, 294 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{16}H_{18}NOP$: C 70.84, H 6.69, N 5.16; found: C 70.86, H 6.52, N 5.22.

Tetrahydrobenzo[*c*][1,2]-2λ^5-azaphosphacycloheptenes (3a and 3b): A solution of *t*BuLi (1.08 mL of a 1.7 M solution in cyclohexane, 1.84×10^{-3} mol) at −90 °C was added to a solution of phosphinamide **1b** (7.38×10^{-4} mol) and DMPU (0.53 mL, 4.42×10^{-3} mol) in THF (30 mL). After 24 h, 2,6-di-*tert*-butyl-4-methylphenol (0.16 g, 3.69×10^{-3} mol) dissolved in 4 mL of THF was added using a cannula. The reaction mixture was stirred at −90 °C for 30 min. Then the mixture was poured into ice water and extracted with ethyl acetate (3×15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. ^1H, $^1H\{^{31}P\}$ and ^{31}P NMR spectra of the crude reaction were measured in order to determine the stereoselectivity of the process. **3a**: Yield = 52% (0.114 g) after chromatography (ethyl acetate/hexane 4:1), identified from a mixture **3a**/**3b** (92:8); oil; ^1H NMR: $\delta = 1.94$ (m, $J = 15.0$, $^3J_{HH} = 6.2$ Hz, 1H; H-5), 2.67 (m, $J = 15.0$ Hz, 1H; H-5′), 2.83 (m, 2H; H-8), 2.90 (d, $J_{PH} = 7.3$ Hz, 3H; H-10), 3.01 (m, 1H; H-5a), 5.02 (ddd, $J_{PH} = 2.9$, $J = 10.3$, $J = 7.0$ Hz, 1H; H-4), 5.57 (dddt, $J_{PH} = 5.5$, $J = 9.9$, $J = 3.3$, $J = 1.9$ Hz, 1H; H-6), 5.72 (m, $J = 9.9$ Hz, 1H; H-7), 5.84 (ddd, $J_{PH} = 9.9$, $J = 10.3$, $J = 1.5$ Hz, 1H; H-3), 7.19 (m, $J_{PH} = 20.6$, $J = 3.7$ Hz, 1H; H-9), 7.58–7.41 (m, 3H), 7.80 ppm (m, 2H); ^{13}C NMR: $\delta = 27.21$ (d, $J_{PC} = 13.8$ Hz; CH_2), 32.97 (CH_2), 35.46 (d, $J_{PC} = 2.4$ Hz; CH_3), 36.39 (d, $J_{PC} = 7.8$ Hz; CH), 113.15 (d, $J_{PC} = 3.6$ Hz; HC=), 123.21 (d, $J_{PC} = 1.8$ Hz; HC=), 128.59 (d, $J_{PC} = 12.5$ Hz; CAr), 129.30 (d, $J_{PC} = 9.6$ Hz; CAr), 130.63 (d $J_{PC} = 128.0$ Hz; C_{ipso}), 131.20 (d, $J_{PC} = 117.7$ Hz; C=), 131.52 (d, $J_{PC} = 10.3$ Hz; CAr), 131.57 (d, $J_{PC} = 2.9$ Hz; CAr), 134.52 (d, $J_{PC} = 1.2$ Hz; HC=), 141.40 ppm (d, $J_{PC} = 6.6$ Hz; HC=); ^{31}P NMR: $\delta = 28.08$; LC-MS (API-ES): *m*/*z* (%): 272 (100) $[M+1]^+$, 271 (22) $[M]^+$, 256 (12); elemental analysis calcd (%) for $C_{16}H_{18}NOP$: C 70.84, H 6.69, N 5.16; found: C 70.79, H 6.77, N 5.15. **3b**: Yield = 22% (0.059 g) after chromatography (ethyl acetate/hexane 4:1), identified from a mixture **3b**/**3a** (74:26); oil; ^1H NMR: $\delta = 2.11$ (ddd, $J =$

13.9, $^{3}J_{HH}$=6.6, J=4.3 Hz, 1H; H-5), 2.61 (m, 1H; H-8,8′), 2.67 (d, J= 7.3 Hz, 3H; H-10), 3.17 (dt, J=13.9, J=6.3 Hz, 1H; H-5′), 3.64 (m, 1H; H-5a), 5.10 (c, J=8.0 Hz, 1H; H-4), 5.66 (m, 2H; H-6,7), 5.85 (m, 2H; H-3,9), 7.51 (m, 3H), 7.79 ppm (m, 2H); ^{13}C NMR: δ=26.96 (d, J_{PC}= 15.0 Hz; CH_2), 31.77 (d, J_{PC}=1.2 Hz; CH_2), 34.73 (d, J_{PC}=4.2 Hz; CH_3), 36.26 (d, J_{PC}=6.6 Hz; CH), 113.30 (d, J_{PC}=1.8 Hz; HC=), 123.13 (d, J_{PC}=1.8 Hz; HC=), 128.40 (d, J_{PC}=12.6 Hz; CAr), 129.16 (d, J_{PC}= 128.0 Hz; C_{ipso}), 129.85 (d, J_{PC}=8.4 Hz; HC=), 131.94 (d, J_{PC}=3.0 Hz; CAr), 133.23 (d, J_{PC}=9.0 Hz; CAr), 133.31 (d, J_{PC}=121.3 Hz; C=), 135.03 (d, J_{PC}=3.0 Hz; HC=), 139.01 ppm (d, J_{PC}=12.6 Hz; HC=); ^{31}P NMR: δ=33.25; LC-MS (API-ES): m/z (%): 272 (100) $[M+H]^+$, 192 (8); elemental analysis calcd (%) for $C_{16}H_{18}NOP$: C 70.84, H 6.69, N 5.16; found: C 70.69, H 6.80, N 5.19.

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