Regio- and Diastereoselective Preparation of Tetrahydrobenzo[*c*]-1-aza-2λ^5-phospholes through Dearomatization Cyclization of Lithiated *N*-Benzyl-*N*-alkyl(diphenyl)phosphinamides. Synthesis of γ-(*N*-Alkylamino)phosphinic Acids

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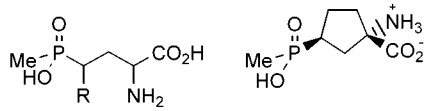
A study of the protonation of the cycloadducts derived from the dearomatization reaction of lithiated *N*-alkyl-*N*-benzyldiphenylphosphinamides has been carried out. The regio- and stereoselectivity of the process has been analyzed in terms of the size of the *N*-alkyl substituent, the acidity and size of the protonating reagent, and the cosolvent used. The optimization of these variables allowed the preparation of tetrahydrobenzo[*c*]-1-aza-2λ^5-phospholes containing a 1,3-cyclohexadiene or 1,4-cyclohexadiene system with moderate to excellent regio- and stereocontrol. The heterocycles were readily hydrolyzed, affording γ-(*N*-alkylamino)diphenylphosphinic acids with the functionalities linked to a cyclohexadiene substructure.

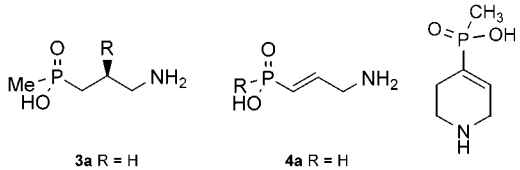
1. Introduction

γ-Aminophosphinic acids and their derivatives are compounds of great interest, due to the relevance of their biological properties.[1] Phosphinothricin **1a** is an important member of this family of compounds. It is a γ-aminophosphinic acid contained in the natural tripeptide bialaphos, currently used as nonselective herbicide.[2] Phosphinothricin analogues **1b,c** and cyclic derivatives **2** have been found to be inhibitors of glutamine synthetase[3] and showed herbicidal activity.[4] The inhibitory activity is assigned to the tetrahedral phosphinic moiety, which is a good transition state mimic in amide formation.[5] γ-Aminophosphinic acids **3a,b** are also effective as $GABA_B$ receptors agonists,[6] while **4a,b**[7] and the cyclic derivative **5**[8] are potent $GABA_C$ receptors antagonists, respectively. However, the syntheses of functionalized derivatives is scarce.[9]



1a R = H
1b R = OH
1c R = Me
Herbicides

2
Herbicide



3a R = H
3b R = OH
$GABA_B$ agonists

4a R = H
4b R = Me

5

$GABA_C$ antagonists

An attractive approach to the preparation of functionalized alicyclic compounds is based on the dearomatization of arenes. This chemistry makes use of stable materials that are widely available and can be readily derivatized. The conjugated π system can be broken up by a number of methods: oxidation,[10] reduction,[11] photocycloaddition,[12] and electrophilic[13] and nucleophilic addition to activated arenes. The activation for the

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(1) Kukhar, V. P.; Hudson, H. R., Eds. *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; John Wiley: New York, 2000.
(2) Bayer, E.; Gugel, K. H.; Haegele, K.; Hagenmaier, H.; Jessipow, S.; Koenig, W. A.; Zaehner, J. *Helv. Chim. Acta* **1972**, *55*, 224.
(3) (a) Johnson, C. R.; Boettcher, B. R.; Cherpeck, R. E.; Dolson, M. G. *Bioorg. Chem.* **1990**, *18*, 154. (b) Logusch, E. W.; Walker, D. M.; McDonald, J. F.; Franz, J. E.; Villafranca, J. J.; Dilanni, C. L.; Colanduoni, J. I.; Li, B.; Schineller, J. B. *Biochemistry* **1990**, *29*, 366.
(4) Logusch, E. W.; Walker, D. M.; McDonald, J. F.; Franz, J. E. *Plant Physiol.* **1991**, *95*, 1057.
(5) (a) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281. (b) Hiratake, J.; Oda, J. *Biosci. Biotech. Biochem.* **1997**, *61*, 211. (c) Valiaeva, N.; Bartley, D.; Konno, T.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 5146.
(6) (a) Nyitrai, G.; Emri, Z.; Crunelli, V.; Kékesi, K. A.; Dobolyi, A.; Juhaász, G. *Eur. J. Pharmacol.* **1996**, *318*, 295. (b) Froestl, W.; Mickel, J. S.; Hall, R. G.; von Sprecher, G.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H. R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297.
(7) Chebib, M.; Vandenberg, R. J.; Froestl, W.; Johnston, G. A. R. *Eur. J. Pharmacol.* **1997**, *329*, 223.
(8) (a) Chebib, M.; Johnston, G. A. R. *J. Med. Chem.* **2000**, *43*, 1427. (b) Chebib, M.; Mewett, K. N.; Johnston, G. A. R. *Eur. J. Pharmacol.* **1998**, *357*, 227.
(9) (a) For a review see: Fields, S. C. *Tetrahedron* **1999**, *55*, 12237. (b) Kehler, J.; Ebert, B.; Dahl, O.; Krogsgaard-Larsen, P. *Tetrahedron* **1999**, *55*, 771. (c) Hanrahan, J. R.; Mewett, K. N.; Shebib, M.; Burden, P. M.; Johnston, G. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2389. (d) Valiaeva, N.; Bartley, D.; Cono, T.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 5146.

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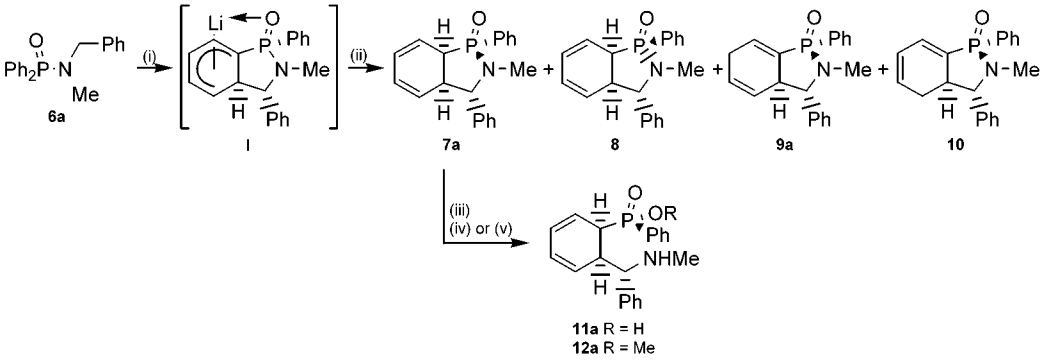
Scheme 1[a]



[a] Conditions: (i) Bu^{s}Li (1.5 equiv), THF, −90 °C, HMPA (6 equiv), 30 min. (ii) MeOH, 30 min. (iii) Chromatography, AcOEt. (iv) 2 N HCl(H_2O), Me_2CO. (v) 0.5 N HCl(g), MeOH.

conjugate addition of nucleophiles to arenes may be induced by complexation to transition metals[14,15] or through bonding to electron-withdrawing groups. Nucleophilic dearomatization of activated benzenes[16] is more difficult than that of naphthalenes[17] or other fused carbocyclic aromatic systems[18] due to the higher resonance stabilization of the benzene ring. Generally, this dearomatization methodology delivers high degrees of chemo-, regio-, and stereocontrol, characteristics that are essential for its application to the synthesis of natural products[19] and nonnatural analogues.[20]

We have recently described the synthesis of γ-(*N*-methylamino)phosphinic acid **11a** and ester **12a** through the stereospecific solvolysis of azaphosphol **7a**. This dearomatized compound was obtained in the anionic cyclization of *N*-benzyl-*N*-methyldiphenylphosphinamide **6a**, followed by quenching with methanol, as a mixture of **7a**:**8**:**9a**:**10** in a 72:5:20:3 ratio in 90% total yield. Column chromatography using ethyl acetate as eluent afforded pure 1-aza-2λ^5-phosphol **7a** (Scheme 1).[21]

The dearomatized compounds **7a** and **9a**, the major components of the reaction mixture, are interesting products. The dihydrobenzene ring of **7a** is stabilized as a 1,3-butadiene system appropriated for Diels−Alder reactions.[22] In **9a** one of the carbon−carbon double bonds of the cyclohexadiene moiety is nucleophilic, while the second one has an electrophilic character, due to the conjugation with the PO linkage. Therefore, these compounds can be considered as scaffolds for the preparation of families of functionalized γ-aminophosphinic acids of wide structural diversity. Moreover, the cyclohexane ring of **7a** and **9a** may be regarded as a constrained element restricting the conformational dynamic of the molecule,[23] an important factor in molecular recognition events.[24] Compounds **7a** and **9a** are the result of moderate regiocontrol in the protonation of the intermediate lithiated species **I** formed in the dearomatizing step (Scheme 1). Considering that this methodology represents a very facile access to conformationally restrained γ-aminophos-

(10) (a) For a review see: Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Arzeno, H.; Barton, D. H. R.; Bergé-Lurion, R. M.; Lusinchi, X.; Pinto, B. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2069. (c) Swenton, J. S.; Carpenter, K.; Chen, Y.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem.* **1993**, *58*, 3308. (d) Quideau, S.; Looney, M. A.; Pouségu, L. *Org. Lett.* **1999**, *10*, 1651. (e) Mandal, S.; Macikenas, D.; Protasiewicz, Sayre, M. L. *J. Org. Chem.* **2000**, *65*, 4804. (f) Pierlot, C.; Poprawski, J.; Marko, J.; Aubry, J. *Tetrahedron Lett.* **2000**, *41*, 5063. (g) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319. For microbial oxidation see: (h) Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Dalton, H.; Chima, J. *J. Am. Chem. Soc.* **1994**, *116*, 1147. (i) Boyd, D. R.; Sharma, N. D.; Bowers, N. I.; Duffy, J.; Harrison, J. S.; Dalton, H. *J. Chem. Soc., Perkin Trans 1* **2000**, 1345. (j) Bui, V.; Hansen, T. V.; Stenstrom, Y.; Ribbons, D. W.; Hudlicky, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1669.

(11) For reviews see: (a) Mander, L. N. *Synlett* **1991**, 134. (b) Donohoe, T. J.; Garg, R.; Stevenson, C. A. *Tetrahedron: Asymmetry* **1996**, *7*, 317. (c) Schultz, A. *Chem. Commun.* **1999**, 1263.

(12) (a) Review: Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615. (b) Noh, T.; Kim, D.; Kim, Y. J. *J. Org. Chem.* **1998**, *63*, 1212. (c) Kohmoto, S.; Masu, H.; Tatsuno, C.; Kishikawa, K.; Yamamoto, M.; Yamaguchi, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4464. (d) Yokoyama, A.; Mizuno, K. *Org. Lett.* **2000**, *2*, 3457.

(13) For reviews see: Harman, W. D. *Chem. Rev.* **1997**, *97*, 1953. (b) Brooks, B. C.; Gunnoe, T. B.; Harman, W. D. *Coord. Chem. Rev.* **2000**, *206−207*, 3−61. (c) Smith, P. L.; Chordia, M. D.; Harman, W. D. *Tetrahedron* **2001**, *57*, 8203. See also: (d) Chordia, M. D.; Harman, W. D. *J. Am. Chem. Soc.* **2000**, *122*, 2725. (e) Fujita, M.; Matsushima, H.; Sugimura, T.; Tai, A.; Okuyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 2946.

(14) (a) Review: Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917. (b) Brooks, B. C.; Gunnoe, T. B.; Harman, W. D. *Coord. Chem. Rev.* **2000**, *206−207*, 3. (c) Smith, P. L.; Chordia, M. D.; Harman, W. D. *Tetrahedron* **2001**, *57*, 8203.

(15) For other metal assisted dearomatizations see: (a) Berger, D.; Imhof, W. *Tetrahedron* **2000**, *56*, 2015. (b) Bao, M.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 759.

(16) (a) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091. (b) Saito, S.; Shimada, K.; Yamamoto, H.; Marigorta, E. M.; Fleming, I. *Chem. Commun.* **1997**, 1299. (c) Brown, D. W.; Lindquist, M.; Mahon, M. F.; Malm, B.; Nilsson, G. N.; Ninan, A.; Sainsbury, M.; Westerlund, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2337 (d) Saito, S.; Sone, T.; Shimada, K.; Yamamoto, H. *Synlett* **1999**, 81. (e) Saito, S.; Sone, T.; Murase, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10216.

(17) For recent references see: (a) Tomioka, K.; Okamoto, T.; Kanai, M.; Yamataka, H. *Tetrahedron Lett.* **1994**, *35*, 1891. (b) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 6437. (c) Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7445. (d) Plunian, B.; Mortier, J.; Vaultier, M.; Toupet, L. *J. Org. Chem.* **1996**, *61*, 5206. (e) Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 5714. (f) Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun.* **1998**, 297. (g) Shimano, M.; Matsuo, A. *Tetrahedron Lett.* **1998**, *54*, 4787. (h) Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103. (i) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351. (j) Shindo, M.; Koga, K.; Asano, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 4955. (k) Kolotuchin, S. V.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3018. (l) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K. I. *J. Org. Chem.* **2001**, *66*, 7051.

(18) (a) James, B.; Meyers, A. I. *Tetrahedron Lett.* **1998**, *39*, 5301. (b) Clayden, J.; Frampton, C. S.; McCarty, C.; Westlund, N. *Tetrahedron* **1999**, *55*, 14161.

(19) (a) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607. (b) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265. (c) Clayden, J.; Tchabanenko, K. *Chem. Commun.* **2000**, 317.

(20) (a) Ahmed, A.; Bragg, R. A.; Clayden, J.; Tchabanenko, K. *Tetrahedron Lett.* **2001**, *42*, 3407. (b) Bragg, R. A.; Clayden, J.; Blandon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411.

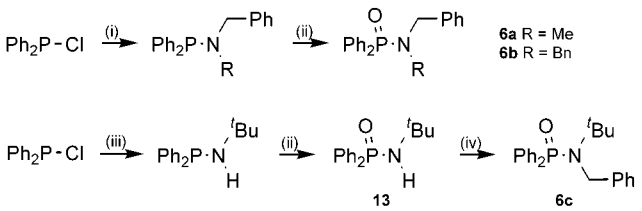
(21) Fernández, I.; López-Ortiz, F.; Tejerina, B.; García-Granda, S. *Org. Lett.* **2001**, *3*, 1339.

(22) Breternitz, H. J.; Schaumann, E.; Adiwidjaja, G. *Tetrahedron Lett.* **1991**, *32*, 1299.

(23) (a) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1. (b) Seebach, D.; Brenner, M.; Rueping, M.; Schweizer, B.; Jaun, B. *Chem. Commun.* **2001**, 207.

(24) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.

Scheme 2[a]



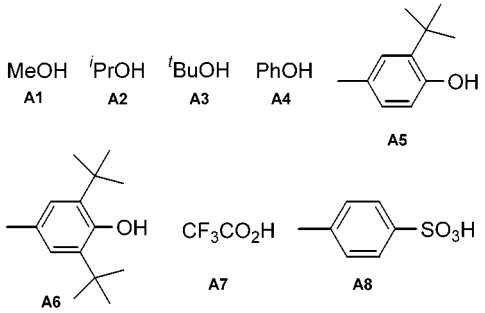
[a] Conditions: (i) HN(Bn)R (R = Me, Bn), Et_3N (2.5 equiv), toluene, 30 min, −78 °C. (i) 30% H_2O_2/THF, 30 min. (iii) Bu^tNH_2, Et_3N (2.5 equiv), toluene, 30 min, −78 °C. (iv) NaH, THF, 30 min, 0 °C, then $PhCH_2Br$, 60 min, rt.

phinic acids,[25] we addressed the goal of optimizing the conditions to achieve the highest regio- and stereoselectivity of the protonation reaction. We focused on two main aspects: the source of the protons and the substituents on the nitrogen atom of the phosphinamide. The results reported in this paper show that it is possible to obtain different tetrahydrobenzo[*c*]-1,aza-2λ^5-phospholes with excellent regio- and stereocontrol by an adequate selection of the protonating agent and the starting phosphinamide. Moreover, preliminary anticancer assays on one of the new azaphospholes obtained showed promising results.

2. Results and Discussion

The phosphinamides **6** were prepared by two methods. For **6a,b**, the appropriated commercial amine was added to a toluene solution of chlorodiphenylphosphine and triethylamine (4 equiv) and the mixture was stirred for 30 min. In situ oxidation with H_2O_2 afforded **6a,b** in 90% yield (Scheme 2).[26] The synthesis of **6c** was carried out through in situ benzylation of *N*-(*tert*-butyl)diphenylphosphinamide **13**,[27] previously obtained following the same procedure used for the preparation of **6a,b**, by treatment with sodium hydride and subsequent addition of benzyl bromide (Scheme 2).[28]

The standard conditions for the dearomatization reaction consisted of the metalation of **6** with 2.5 equiv of *s*-BuLi at −90 °C during 30 min in the presence of HMPA (6 equiv).[29] The protonation was carried out also at −90 °C by addition to the reaction mixture of a solution of the reagent in THF via cannula. After stirring for 30 min, the reactions were processed through conventional aqueous workup. First, the reaction with **6a** was used as reference to identify the quenching reagent giving the best regio- and diastereoselectivity ratios. Then, these reagents were applied to the remaining phosphinamides to analyze the effect of the substitution at the nitrogen. The acids **A1**−**A8** used for the protonation reaction are represented above. The reaction time with **A8** was increased to 12 h, due to its insolubility under the conditions essayed. They were selected on the basis of two criteria: (i) a broad range of pK_a values should be covered ($\Delta pK_a = \sim 25$), and (ii) they should reveal possible steric effects. The structures of the 1-aza-2λ^5-phospholes obtained in this study are shown in Scheme 3.



Structural Characterization. Compounds **7a**−**10a** have been characterized previously.[21] The new derivatives **14**−**16** were isolated by column chromatography and identified through their NMR data.[30] As a rule, protonation of intermediate species **I** at the α or γ position to the phosphorus can be easily established by inspection of the ^1H, $^1H\{^{31}P\}$, and ^{13}C NMR spectra. 1,4-Cyclohexadiene derivatives were characterized by the signal of the C_β-H to the phosphorus. This proton is deshielded due to the conjugation of the carbon−carbon double bond with the PO linkage and appeared as a multiplet at $\delta > 6.6$ ppm showing a large coupling with the phosphorus, $^3J_{PH} > 16$ Hz. The olefinic protons of the 1,3-cyclohexadiene moiety absorbed at $\delta < 6.5$ ppm and the ^{13}C spectra showed a doublet of $^1J_{PC} > 75$ Hz for the methine carbon linked to the phosphorus ($\delta < 45$ ppm), a ^{31}P,^{13}C coupling remarkably large for a sp^3 carbon. On the other hand, compared to **7a** and **9a**, the inversion of the configuration of the methine carbon linked to the nitrogen of **15** and **16** was accompanied by the appearance of a $^3J_{PH}$ in the proton spectrum. The trans junction of the bicyclic system of **14** and **15** was identified by the large vicinal coupling between the bridgehead protons, $^3J_{HH}^{trans} > 20$ Hz.[31] In all cases, the configurations assigned were confirmed through the respective NOESY spectra.

(25) Chebib, M.; Johnston, G. A. R. *Clin. Exp. Pharmacol. Physiol.* **1999**, *26*, 937.

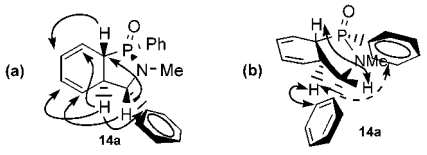
(26) This is a slight modification of the method described for the synthesis of **6b** by Edmunson, R. S.; Moran, T. A. *J. Chem. Soc.* **1970**, 1009.

(27) (a) Smith, N. L.; Sisler, H. H. *J. Org. Chem.* **1961**, *26*, 5145. (b) Modro, T. A.; Lawry, M. A.; Murphy, E. *J. Org. Chem.* **1978**, *43*, 5000.

(28) An analogous method has been described for the preparation of **5a**, Coulton, S.; Moore, G. A.; Ramaje, R. *Tetrahedron Lett.* **1976**, 4005.

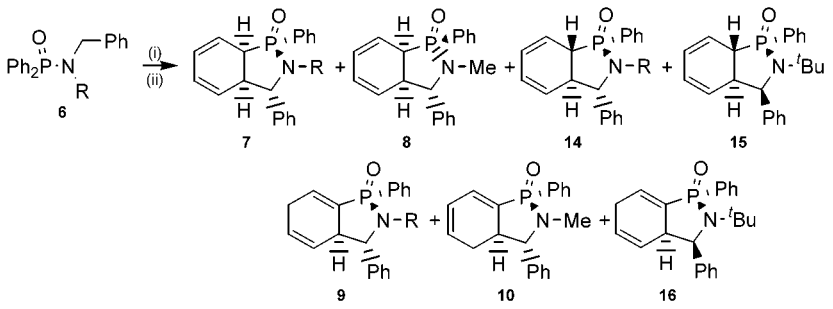
(29) For related intramolecular dearomatization of activated benzenes see: (a) Hauser, C. R.; Eenam, D. N. V. *J. Am. Chem. Soc.* **1957**, *79*, 5512. (b) Hayashi, Y.; Oda, R. *Tetrahedron Lett.* **1968**, 5381. (c) Negishi, E.; Merrill, R. E. *J. Chem. Soc., Chem. Commun.* **1974**, 860. (d) Shirai, N.; Sumiya, F.; Sato, Y.; Hori, M. *J. Org. Chem.* **1989**, *54*, 836. (e) Bolton, R. E.; Moody, C. J.; Rees, C. W. *J. Chem. Soc. Perkin Trans. 1* **1989**, 2136. (f) Crandall, J. K.; Ayers, T. A. *J. Org. Chem.* **1992**, *57*, 2993. (g) Padwa, A.; Filipkowski, M. A.; Kline, D. N.; Murphree, S.; Yeske, P. E. *J. Org. Chem.* **1993**, *58*, 2061. (h) Citterio, A.; Sebastiano, R.; Maronati, R. S.; Bergamini, F. *J. Chem. Soc., Perkin Trans 1* **1994**, 1517. (i) Brown, D. W.; Lindquist, M.; Mahon, M. F.; Malm, B.; Nilsson, G. N.; Ninan, A.; Sainsbury, M.; Westerlund, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2337. (j) Berger, R.; Ziller, J. W.; van Vranken, D. L. *J. Am. Chem. Soc.* **1998**, *120*, 841. (k) Aggarwal, V. K.; Ferrara, M. *Org. Lett.* **2000**, *2*, 4107. (l) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Org. Lett.* **2000**, *2*, 4229 and references therein. (m) Clayden, J.; Tchabanenko, K.; Yasin, S. A.; Turnbell, M. D. *Synlett* **2001**, 302.

(30) The structural assignment was based on the analysis of the 1D (^1H, ^{13}C, ^{31}P, DEPT, selective TOCSY) and 2D (gHMQC, gHMBC and gNOESY) spectra. Key correlations observed in the (a) HMBC and (b) NOESY spectrum of **14a** are shown below. The HMBC spectrum afforded the connectivity of the molecule, while the configuration was obtained from the NOESY spectrum.



(31) Measured in the $^1H\{^{31}P\}$ spectrum from the proton α to the phosphorus atom, which appears at δ 3.0 ppm.

Scheme 3[a]



[a] Conditions: (i) Bu^{s}Li (1.5 equiv), THF −90 °C, HMPA (6 equiv), 30 min. (ii) **A1**−**A8**, −90 °C, THF, 30 min (for **A8**, 12 h).

Table 1. Distribution of Dearomatized Products (in %) Derived from 6a and A1−A8 Acids

acid	7a	8a	9a	10a	14a	% yield
A1	72	5	20	3		90
A2	53	2	25	3		83
A3	40		56	4		74
A4	24	3	70		3	82
A5	40		56		4	77
A6			>97			>97
A7	16	3	49		32	89
A8	16	8	24	2	50	84

Additionally, crystals of **9a** suitable for X-ray analysis were grown by recrystallization from hexane/dichloromethane.[32] The molecular structure is shown in Figure S4 (see Supporting Information) and confirms the assignment of the configuration of the stereogenic centers of the molecule made from the NMR data.

Protonation Studies. The distribution of products for a given combination of phosphinamide **5a** and quenching reagent is collected in Table 1.[33] Methanol showed the lowest regioselectivity of all alcohols assayed, affording a reaction mixture composed by the regioisomers corresponding to the protonation in all possible positions derived from the delocalization of the negative charge. However, protonation at the α position to the phosphorus was the preferred site. In fact, methanol proved to be the best acid for obtaining **7a** in good yield. As shown by the series of alcohols **A1**−**A3** and **A4**−**A6**, the increase of the size of the carrier of the OH favored the formation of the nonconjugated cyclohexadiene compound **9a** through γ-attack to the phosphorus (entries 1−6). Even though, the ratio **9a**:**7a** do not increase linearly with increasing hindrance around the OH group (see entries 3−5). The reaction with 2,6-di-*tert*-butyl-4-methylphenol **A6** is really outstanding, because **9a** containing three stereogenic centers was obtained quantitatively with total regio- and stereoselectivity.

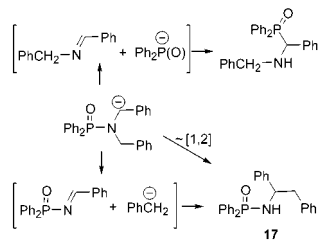
In the protonation reactions with phenol (**A4**) and 2-*tert*-butyl-4-methylphenol (**A5**), a new product, **14a**, was formed, although in very low yield. Interestingly, the yield of **14a** increased notably when stronger organic acids were used as quenching reagents. Thus, trifluoroacetic acid (**A7**) gave a mixture of **7a**:**8a**:**9a**:**14a** in a ratio 16:3:49:32 in 89% total yield (entry 6), i.e., 28% of **14a**, and this compound was the major component of the reaction with *p*-toluensulfonic acid (**A8**), which allowed us to obtain the azaphosphole **14a** in reasonable yield (42%, entry 7). Considering that the protonation reaction is irreversible, the products obtained would correspond to a kinetically controlled reaction. From the data collected in Table 1, one can conclude that the acids **A1**, **A6**, and **A8** are the best choice for the synthesis of the azaphospholes **7a**, **9a**, and **14a**, respectively, in the anionic dearomatization of **6a**. Therefore, these acids were used as protonating reagents in the analogous reaction with phosphinamides **6b,c**. The results obtained are shown in Table 2, including those of **6a** for comparison. A glimpse of the performance of the protonation with **A1** and **A6** can be obtained from Figures 1 and 2, respectively. A graphical representation of the reactions with **A8** is given in Figure S1 (Supporting Information).

The reactions of dibenzylphosphinamide **6b** followed the same trends outlined for **6a**, although with improved regio- and stereoselectivity: protonation ϵ to the phosphorus did not occur and the 1,3-cyclohexadiene derivatives **8b** and **14b** were not observed. Yields were slightly lower due to the formation of a second[33] byproduct **17** in less than 10%.[34,35] Under standard conditions, i.e., an excess of base and HMPA, an additional decrease of the reaction yield was caused by the formation of **19** and **20** (Table S1, Supporting Information). These products were derived from the metalation of the benzyl substituent of **7b** and **9b** and subsequent addition of the new anions to the *N*-methylmethyleneimine **18** arising from the deprotonation of the HMPA (Scheme 4).[36]

(32) Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 172030. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [Fax: +44(0)-1223-336033. E-mail: deposit@ccdc.cam.ac.uk].

(33) In all assays small amounts (<7%) of $Ph_2P(O)Bu^s$, formed by nucleophilic attack of the base to the starting phosphinamide, were observed.

(34) The byproduct **17** was isolated and identified as $Ph_2P(O)NHCH(Ph)CH_2Ph$. Formation of **17** may be explained through a [1, 2] rearrangement of the benzylic anion generated in the metalation of **6b**, a process competing with the dearomatization reaction: (a) Eisch, J. J.; Dua, S. K.; Kovacs, C. A. *J. Org. Chem.* **1987**, *52*, 4437. (b) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981. (c) Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1275. (d) Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817. The participation of an imine intermediate through a β-elimination process of the benzylic anion is not probable because the diphenylphosphinoyl moiety would be more prone to the elimination than the benzyl group, see ref 23.



(35) Savignac, P.; Leroux, Y. *J. Organomet. Chem.* **1973**, *57*, C47.

Table 2. Product Distribution in the Dearomatization−Protonation Reactions of 6a−c[a]

acid	7a	7b	7c	9a	9b	9c	14a	14b	14c	16a	16b	16c
A1	72 (90)	62 (80)[b]	46 (62)	20[c]	22	19						27[d]
A6				>97 (97)	>97 (97)[b]	79 (77)						21
						88 (78)[b]						12
A8	16 (84)	18 (79)[b]	28 (74)	24[f]	82	23	50		29			16[e]

[a] Numbers in parentheses indicate reaction total yields. [b] Using DMPU as cosolvent. [c] Also obtained **8** (5%) and **10** (3%). [d] A 7% of **15** was also formed. [e] A 4% of **15** was also formed. [f] A 8% of **8** was also formed. **a**: R= Me; **b**: R= Bn; **c**: R= *t*Bu.

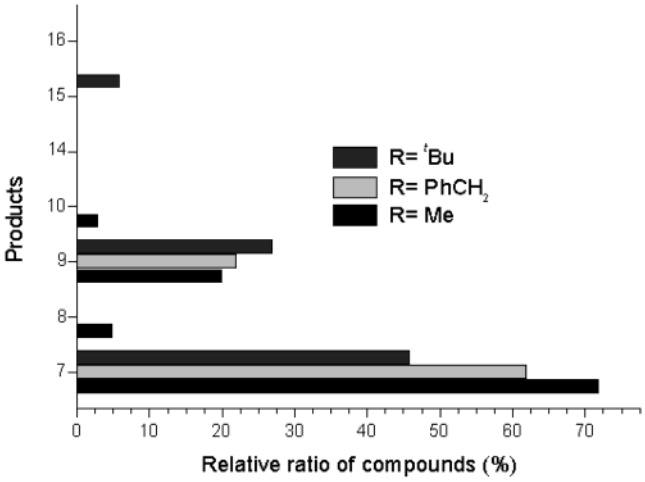


Figure 1. Distribution of products for the protonation with methanol. Data correspond to the use of DMPU as cosolvent for R = $PhCH_2$.

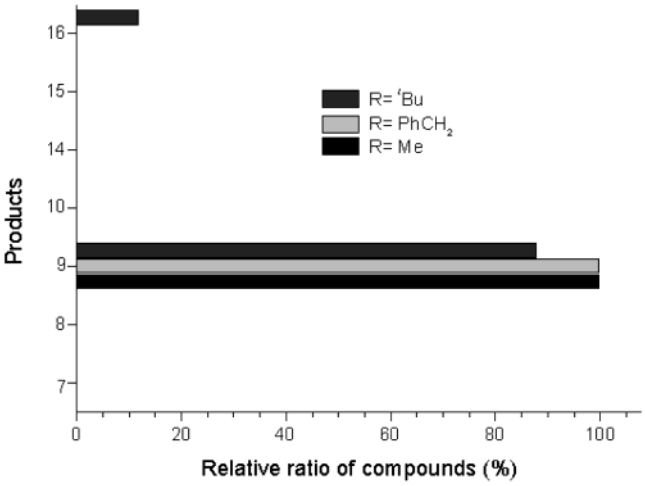
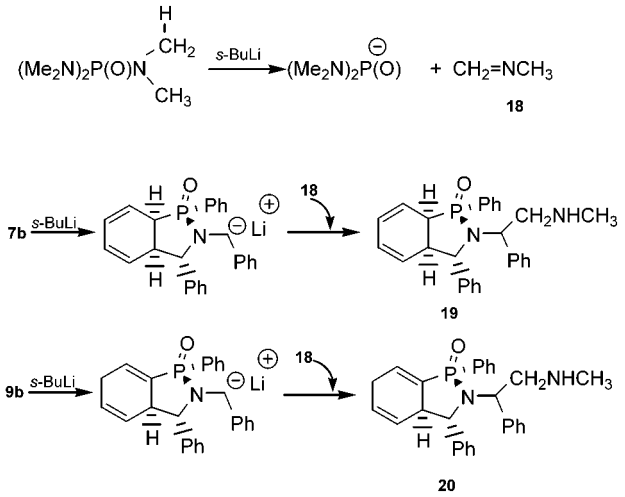


Figure 2. Distribution of products for the protonation with 2,4-di-*tert*-butyl-4-methylphenol. Data correspond to the use of DMPU as cosolvent for R = $PhCH_2$ and *t*-Bu.

Fortunately, this side reaction was completely suppressed by using DMPU instead of HMPA as cosolvent. As expected, methanol was the best proton source for obtaining **7b**. The ratio **7b**:**9b** was lower than that of the *N*-methyl series, although **7b** could be still isolated in fairly good yield (50%). The protonation with phenol **A6** was again exceptionally efficient, affording compound **9b** with total regio- and stereocontrol in quantitative yield; i.e., no rearranged byproduct was formed. On the contrary, *p*-toluenesulfonic acid (**A8**) proved to be useless for

(36) Similar transformations of HMPA under strong basic conditions have been previously reported: (b) Abatjoglou, A. G.; Eliel, E. L. *J. Org. Chem.* **1974**, *39*, 3042. (c) Magnus, P.; Roy, G. *Synthesis* **1980**, 575.

Scheme 4



obtaining **14b**; the crude reaction was composed exclusively of a mixture of **7b**:**9b** in a ratio 18:82.

In the series of phosphorus compounds studied, phosphinamide **6c** has the bulkiest substituent linked to the nitrogen. A positive consequence of this bulkiness was prevention of the attack of the base to the PO linkage, avoiding the formation of phosphine oxide byproducts.[33] Similar to **6b**, neither compound **8c** nor compound **10c** was formed. With regard to **6a**, the large size of the Bu^t produced a decrease in both the stereoselectivity of the process and the reaction yield. Doubling the time of the metalation step modifies neither the yield nor the distribution of products appreciably. The general trends previously mentioned for **6a** were maintained: azaphospholes **7c**, **9c**, and **14c** were preferentially formed by quenching with acids **A1**, **A6**, and **A8**, respectively, even though **7c** was obtained in low yield (29%) and **14c** was a component of a mixture of five compounds **7c**:**9c**:**14c**:**15c**:**16c** (ratio, 28:23:29:4:16). The stereoselectivity of the reaction with **A6** was much higher, affording a mixture of **9c**:**16c** in a ratio 79:21 that increased to 88:12 when DMPU was used as cosolvent. The change in the cosolvent did not affect the reaction yield.

It is worth mentioning that in all cases significant amounts of a new stereoisomer of the 1,4-cyclohexadiene series, **16c**, were present. This compound is an epimer of **9c** in the carbon linked to the nitrogen. It can be assumed that the stereocontrol of that position will be sensitive to steric hindrance derived from the bulkiness of the *N*-R group of the phosphinamide. Accordingly, the largest effect was observed for R = Bu^t. The fact that the yield of **16c** tends to increase in the series Me ≪ $PhCH_2$ < Bu^t indicates that the transition state energy differences of the dearomatizing steps leading to lithiated **9** and **16** decrease along that series. Another consequence of increasing the size of R is the increase of the ratio **9**:**7**, i.e., protonation γ vs α to the phosphorus, which also follows the series Me < $PhCH_2$ < Bu^t. In principle, these

Scheme 5

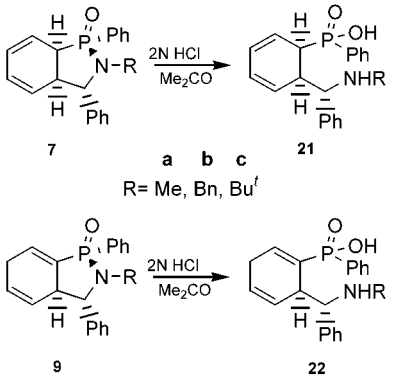


Table 3. δ ^{31}P (ppm) of Compounds 21 and 22

acid	**21a**	**21b**	**21c**	**22a**	**22b**	**22c**
δ	28	26.4	24.6	34	29.4	28.7

purely steric effects cannot be assigned to possible interactions between the R group and the incoming acid, because they are each too far away from the protonation sites (see Figure S4). A reasonable explanation would be to assume that the approach of the quenching reagent to an intermediate **I** (Scheme 1) is directed by coordination to the lithium cation, which is also coordinated to the PO group of the molecule.[37] The increase in the bulkiness of R would force the phenyl ring bonded to the phosphorus to move away from R to alleviate steric repulsions. This conformational change would increase the PO···Li distance in the contact ion pair **I**, thus eroding the directing power of the PO linkage and, as a consequence, favoring the protonation at the γ site.

To show the utility of the present methodology for the synthesis of γ-aminophosphinic acids, the dearomatized compounds **7** and **9** were treated with 2 N HCl in acetone. As anticipated, the hydrolysis of the P−N bond was almost instantaneous. The corresponding γ-(*N*-alkylamino)phosphinic acids **21** and **22** were obtained in quantitative yields without affecting the cyclohexadiene system (Scheme 5, Table 3).

The ^{1}H NMR spectra revealed the leakage of the P−N bond through the loss of the phosphorus coupling with the protons and/or carbons of the R substituent. The presence of one amino functional group and one acid produced a broadening of all signals of the spectrum. Interestingly, the increase of the size of the *N*-alkyl substituent produced an upfield shift of δ ^{31}P of the aminophosphinic acids. Considering the four-bond separation of the NHR moiety of **21** and **22** from the phosphorus atom, the effect of the *N*-substituent on the ^{31}P chemical shift suggest that **21** and **22** are stabilized in the form of zwitterions with a close contact between the polar phosphinate and ammonium groups. For amino acids **21**, the small vicinal coupling between the protons linked to the sp^3 carbons of the cyclohexadiene moiety and the correlations observed in the NOESY spectra indicated that no epimerization at the C_α to the phosphorus occurred during the hydrolysis step.

Conclusions. Optimized conditions have been found for the regio- and stereoselective protonation reaction of the anionic dearomatized cycloadducts of *N*-alkyl-*N*-benzyldiphenylphosphinamides. Kinetic acidity and steric interactions are the two major factors controlling the outcome of the process. Protonation α to the phosphorus occurs preferably with methanol, affording azaphospholes fused to a 1,3-cyclohexadiene system in isolated yields ranging 29% to 65%. 2,6-Di-*tert*-butyl-4-methylphenol is the acid of choice for protonation at the γ position to the phosphorus, giving rise to 1,4-cyclohexadiene derivatives with excellent regio- and stereoselectivities and yields. For **6b,c**, the best results were obtained when DMPU was used as cosolvent, instead of HMPA. On the other hand, a moderate yield of **14a** could be obtained when *p*-toluensulfonic acid was used as quenching reagent in the anionic cyclization of phosphinamide **6a**. It is interesting to mention that azaphosphole **9b** showed promising growth cell inhibition (factors higher than 50%, concentration of 1.1×10^{-4} M) against three human tumor cell lines (lung, breast, central nervous system).[38] The heterocycles were easily hydrolyzed by treatment with dilute acid.

The overall synthetic sequence represents an efficient methodology for the preparation of γ-(*N*-alkylamino)-phosphinic acid containing a 1,3- or 1,4-cyclohexadiene substructure using very simple reagents. This moiety can be envisioned as an element of conformational constraint and further functionalization, two important characteristic for their application in peptidomimetic chemistry.[39] Further work in this field is in progress.

Experimental Section[40]

X-ray. A colorless crystal approximately 0.30 × 0.23 × 0.13 mm was used for the measurements at 293(2) K. The unit-cell dimensions were determined from the angular settings of 25 reflections in the range $15 \le \theta \le 18°$. The space group was inferred to be $P2_1/n$ from systematic absences. Unit-cell data: $a = 9.637(3)$ Å, $b = 15.372(5)$ Å, $c = 11.719(2)$ Å, $\beta = 101.85(4)°$, $V = 1699.0(8)(7)$ Å^3, $Z = 4$, $D_x = 1.256$ Mg/m^3, $\lambda = 0.071073$ Å, $\mu = 0.166$ mm^{-1}, $F(000) = 680$.

The intensities of 3541 reflections in the range 0°−26° and in the range $-11 \le h \le 0$, $-18 \le k \le 0$, $-14 \le l \le 14$ were measured using the $\omega\angle 2\theta$ scan technique with a scan angle of 1.5° and a variable scan rate with a maximum scan time of 60 s per reflection. Mo Kα radiation was used with a graphite-crystal monochromator on a Nonius CAD4 single-crystal diffractometer. The intensity of the primary beam was checked throughout the collection by monitoring three standard reflections every 60 min. On all reflections, profile analysis was performed,[41] and 2279 were observed with $I > 2\sigma(I)$. Lorentz and polarization corrections were applied.

The structure was solved by direct methods using SHELXS97.[42] An empirical absorption correction was applied at this stage, using XABS2.[43] The relative maximum and minimum transmission factors were 0.953 and 0.975, respectively. The H-atoms were geometrically placed and refined,

(37) (a) Reich, H. J.; Barst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728. (b) Mohrig, J. R.; Lee, P. K.; Stein, K. A.; Mitton, M. J.; Rosenberg, R. E. *J. Org. Chem.* **1995**, *60*, 3529. (c) Yadav, V. K.; Jeyaraj, D. A. *J. Org. Chem.* **1998**, *63*, 3474.

(38) Assays for potential chemotherapeutic agents were carried out at the National Cancer Institute, Bethesda, MD.

(39) (a) Verbruggen, C.; De Craecker, S.; Rajan, P.; Jiao, X.-Y.; Boloo, M.; Smith, K.; Fairlamb, A. H.; Haemers, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 253. (b) Schiodt, C. B.; Buchardt, J.; Terp, G. E.; Christensen, U.; Brink, M.; Larsen, Y. B.; Meldal, M.; Foged, N. T. *Curr. Med. Chem.* **2001**, *8*, 967. (c) Woll, M. G.; Lai, J. R.; Guzei, I. A.; Taylor, S. J. C.; Smith, M. E. B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 11077.

(40) For general experimentals, see the Supporting Information in ref 21.

(41) (a) Grant, D. F.; Gabe, E. J. *J. Appl. Crystallogr.* **1978**, *11*, 114. (b) Lehman, M. S.; Larsen, F. K. *Acta Crystallogr. A* **1974**, *30*, 580.

(42) Sheldrick, G. M. *SHELXS-97, Program for the Solution of Crystal Structures*; University of Göttingen: Germany, 1997.

(43) Parkin, S.; Moezzi, B.; Hope, H. *J. Appl. Crystallogr.* **1995**, *28*, 53. (b) Nardelli, M. *Comput. Chem.* **1983**, *7*, 95.

riding with common isotropic thermal parameters. During the final stages of the refinements, all positional parameters and the anisotropic temperature factors of all the non-H atoms were refined using SHELXL97.[44] The final agreement factors are $R = 0.056$ and wR = 0.162, $S = 1.006$ for the 2279 "observed" reflections and 212 variables. The function minimized was $([\sum wF_o^2 - F_c^2)/\sum w(F_o^2)]^{1/2}$,where $w = 1/[\sigma^2(F_o^2) + (0.1363P)^2]$ with $\sigma(F_o^2)$ from counting statistics and $P = (\text{Max}(F_o^2,0) + 2F_c^2)/3$. The maximum shift-to-error ratio in the final full-matrix least-squares cycle was 0.000, while the highest and lowest peaks in the final difference Fourier calculated were 0.43 and −0.52 e Å^{-3}.

Atomic scattering factors were taken from *International Tables for X-ray Crystallography*.[45] Plots were made with the EUCLID package.[46] Geometrical calculations were made with PARST.[47] All calculations were made at the Scientific Computer Centre of the University of Oviedo and on the X-ray group DEC/AXP− computers.

General Procedure for the Preparation of Phosphinamides 6a,b. To a solution of chlorodiphenylphosphine (2.69 mL, 15.03 mmol) and triethylamine (5.21 mL, 37.6 mmol) in toluene (100 mL) at −30 °C was added the appropiate amine (2.00 mL). The mixture was stirred during 4 h and then 30% v/v H_2O_2 (1.7 mL, 15.03 mmol) was added. Once the oxidation was completed (1 h), the reaction was poured into ice water and extracted with ethyl acetate (3 × 15 mL) and washed with 1 N NaOH (2 × 15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo, affording **6a,b** as white solids. The purity of the phosphinamides was higher than 97% (NMR), and the compounds were used without further purification in the next synthetic steps. Alternatively, they can be precipitated from Et_2O. Phosphinamides **6a** and **6b** have been previously described: **6a**, mp 82−83 °C, lit.[28] mp 82−83 °C; **6b**, mp 125−126 °C, lit.[26] mp 126−127 °C.[26]

***N*-Benzyl-N-tert-butyldiphenylphosphinamide (6c).** To a solution of chlorodiphenylphosphine (3.6 mL, 19.03 mmol) and triethylamine (6.6 mL, 47.57 mmol) in toluene (100 mL) at −30 °C was added the appropiate amine (2.00 mL). The mixture was stirred during 4 h and then 30% v/v H_2O_2 (2.2 mL, 19.03 mmol) was added. Once the oxidation was completed (1 h), the reaction was poured into ice water and extracted with ethyl acetate (3 × 15 mL) and washed with 1 N NaOH (2 × 15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo, affording **13** as a white solid (yield 97%). Then, **13** (5.0 g, 18.31 mmol) was treated at room temperature with HNa (1.3 g, 36.62 mmol) in THF during 30 min, and then benzyl bromide (2.2 mL, 18.31 mmol) was added at the same temperature (1 h), affording, after an identical workup as done before, **6c** as a white solid. The purity of the phosphinamide was higher than 97% (NMR) and the compound was used without further purification in the next synthetic steps. Alternatively, it can be precipitated from Et_2O:

yield 90−95%; mp 151−153 °C; ^{1}H NMR δ 1.40 (s, 9H), 4.30 (d, CH_2, J_{PH} 15.4 Hz), 7.39−7.10 (m, 6H, ArH), 7.76 (m, 4H, ArH);^{13}C NMR δ 30.87 (d, CH_3, J_{PC} 3.3 Hz), 49.62 (d, CH_2, J_{PC} 4.5 Hz), 58.65 (d, C, J_{PC} 1.2 Hz), 126.16−130.95 (6CAr), 132.08 (d, CAr, J_{PC} 9.5 Hz), 134.85 (d, C_{ipso}, J_{PC} 126.5 Hz), 141.35 (d, C_{ipso}, J_{PC} 1.7 Hz); ^{31}P NMR δ 32.14; MS (API-ES) *m/e* 364 (M + 1, 100), 308 (10). Anal. Calcd (%) for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.85. Found: C, 76.06; H, 7.12; N, 3.82.

General Procedure for the Preparation of Tetrahydrobenzo[c]-1-aza-2λ^5-phospholes. To a solution of the appropriate phosphinamide (6.23×10^{-4} mol) and HMPA (3.72×10^{-3} mol) in THF (30 mL) was added a solution of *s*-BuLi (1.2 mL of a 1.3 M solution in cyclohexane, 1.56×10^{-3} mol) at −90 °C. After 30 min of metalation was added the corresponding proton source (3.12×10^{-3} mol). The reaction mixture was stirred at −90 °C for 30 min, except for *p*-toluenesulfonic acid, where the time increased to 12 h due to insolubility problems. Then the reaction 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. ^{1}H, ^{1}H{^{31}P}, and ^{31}P NMR spectra of the crude reaction were measured in order to determine the stereoselectivity of the process. The reaction mixture was then purified by flash column chromatography using different mixtures of ethyl acetate:hexane as eluent.

The same procedure was applied when the reaction was carried out in the presence of DMPU (3.72×10^{-3} mol) as cosolvent. Azaphospholes **7a**−**10a** have been characterized previously.[21]

(2*S*$_P$R**$_P$,3*RS*,8*RS*,9*SR*)-2,3,4,9-Tetrahydro-*N*-benzyl-3-phenylbenzo[c]-1-aza-2λ^5-phosphole 2-oxide (7b):** yield after chromatography (ethyl acetate) 52% (0.104 g, protonation with **A1**); mp 135−137 °C; ^{1}H NMR δ 3.01 (m, 1H, J_{PH} 3.7, *J* 9.9, *J* 10.6 Hz), 3.21 (m, 1H, J_{PH} 11.9, *J* 10.6 Hz), 3.69 (dd, 1H, J_{PH} 12.6, *J* 14.7 Hz), 4.14 (d, 1H, *J* 9.2 Hz), 4.30 (dd, 1H, J_{PH} 8.9, *J* 14.7 Hz), 5.41 (m, 1H, *J* 9.5, *J* 5.5, *J* 0.8 Hz), 5.99 (dd, 1H, *J* 9.5, *J* 5.1 Hz), 6.19−6.07 (m, 2H), 7.56−7.13 (m, 13H, ArH), 7.97 (m, 2H, ArH); ^{13}C NMR δ 37.62 (d, CH, J_{PC} 84.7 Hz), 43.01 (CH), 45.94 (d, CH, J_{PC} 3.0 Hz), 66.84 (d, CH, J_{PC} 21.6 Hz), 119.44 (d, HC=, J_{PC} 8.4 Hz), 123.65 (d, HC=, J_{PC} 11.4 Hz), 124.57 (d, HC=, J_{PC} 3.0 Hz), 124.73 (d, HC=, J_{PC} 10.2 Hz), 131.75−126.99 (12CAr), 131.57 (d, CAr, J_{PC} 10.2 Hz), 131.74 (d, CAr, J_{PC} 2.4 Hz), 134.17 (d, C_{ipso}, J_{PC} 126.2 Hz), 136.18 (C_{ipso}), 139.30 (d, C_{ipso}, J_{PC} 9.0 Hz); ^{31}P NMR δ 50.38; MS (API-ES) *m/e* 398 (M + 1, 100), 230 (12), 196 (20), 91 (10). Anal. Calcd (%) for $C_{26}H_{24}NOP$: C, 78.57; H, 6.08; N, 3.52. Found: C, 78.51; H, 6.12; N, 3.32.

(2*S*$_P$R**$_P$,3*RS*,8*RS*,9*SR*)-2,3,4,9-Tetrahydro-*N*-*tert*-butyl-3-phenylbenzo[c]-1-aza-2λ^5-phosphole 2-oxide (7c):** yield after chromatography (ethyl acetate:hexane 1:1) 28% (0.056 g, protonation with **A1**); identified from a mixture **7a**:**7c** (66:34); mp 135−136 °C. ^{1}H NMR δ 1.21 (s, 9H), 3.02 (dddd, 1H, J_{PH} 11.6, *J* 10.3, *J* 4.8, *J* 1.8 Hz), 3.19 (m, 1H, J_{PH} 24.4 Hz), 4.74 (dd, 1H, J_{PH} 4.1, *J* 4.8 Hz), 5.61 (dd, 1H, *J* 9.5, *J* 4.0 Hz), 5.75 (m, 1H), 6.03 (dd, 1H, *J* 10.3, *J* 5.5 Hz), 6.12 (m, 1H), 7.77−7.01 (m, 8H, ArH), 8.02 (m, 2H, ArH); ^{13}C NMR δ 30.46 (d, CH_3, J_{PC} 3.0 Hz), 37.61 (d, CH, J_{PC} 78.7 Hz), 44.24 (d, CH, J_{PC} 1.2 Hz), 57.01 (C), 68.05 (d, CH, J_{PC} 20.4 Hz), 119.54 (d, HC=, J_{PC} 8.4 Hz), 125.62 (d, HC=, J_{PC} 4.8 Hz), 125.88 (d, HC=, J_{PC} 10.2 Hz), 126.54 (d, HC=, J_{PC} 5.4 Hz), 132.45−125.98 (10CAr), 134.85 (d, C_{ipso}, J_{PC} 126.8 Hz), 145.60 (d, C_{ipso}, J_{PC} 6.6 Hz); ^{31}P NMR δ 47.79; MS (API-ES) *m/e* 365 (M + 2, 75), 364 (M + 1, 100). Anal. Calcd (%) for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.85. Found: C, 76.11; H, 7.22; N, 3.62.

(2*S*$_P$R**$_P$,8*RS*,9*SR*)-2,3,4,7-Tetrahydro-*N*-benzyl-3-phenylbenzo[c]-1-aza-2λ^5-phosphole 2-oxide (9b):** yield after chromatography (ethyl acetate) 94% (0.188 g, protonation with **A5**); mp 172−175 °C; ^{1}H NMR δ 2.77 (m, 1H, *J* 23.1, *J* 5.1, *J* 2.6 Hz), 2.92 (m, 1H, *J* 23.1 Hz), 3.30 (m, 1H), 3.65 (dd, 1H, J_{PH} 13.9, *J* 14.7 Hz), 3.95 (d, 1H, *J* 9.5 Hz), 4.29 (dd, 1H, J_{PH} 8.8, *J* 14.7 Hz), 5.51 (m, 1H, *J* 9.9 Hz), 5.73 (m, 1H, *J* 9.9 Hz, *J* 1.5 Hz), 6.78 (d, 1H, J_{PH} 16.9 Hz), 7.57−7.13 (m, 13H, ArH), 8.01 (m, 2H, ArH);^{13}C NMR δ 27.67 (d, CH_2, J_{PC} 12.8 Hz), 45.95 (d, CH_2, J_{PC} 3.1 Hz), 46.38 (d, CH, J_{PC} 13.9 Hz), 66.18 (d, CH, J_{PC} 12.6 Hz), 122.78 (d, HC=, J_{PC} 6.4 Hz), 125.02 (d, HC=, J_{PC} 1.7 Hz), 131.80−127.94 (15CAr), 132.79 (d, C=, J_{PC} 121.8 Hz), 133.87 (d, C_{ipso}, J_{PC} 133.6 Hz), 135.63 (d, HC=, J_{PC} 9.7 Hz), 136.12 (C_{ipso}), 138.51 (d, C_{ipso}, J_{PC} 8.3 Hz); ^{31}P NMR δ 29.76; MS (API-ES) *m/e* 398 (M + 1, 100), 91 (6). Anal. Calcd (%) for $C_{26}H_{24}NOP$: C, 78.57; H, 6.08; N, 3.52. Found: C, 78.71; H, 6.10; N, 3.42.

(2*S*$_P$R**$_P$,8*RS*,9*SR*)-2,3,4,7-Tetrahydro-*N*-tert-butyl-3-phenylbenzo[c]-1-aza-2λ^5-phosphole 2-oxide (9c):** yield after chromatography (ethyl acetate:hexane 1:1) 69% (0.137 g, protonation with **A5**); oil; ^{1}H NMR δ 1.17 (s, 9H), 2.71 (ddddd, 1H, J_{PH} 4.8, *J* 22.7, *J* 12.5, *J* 4.8, *J* 2.6 Hz), 2.88 (m, 1H), 3.22 (m, 1H), 4.33 (d, 1H, *J* 9.6 Hz), 5.45 (m, 1H, *J* 9.6 Hz), 5.74 (m, 1H), 6.63 (m, 1H, J_{PH} 16.2 Hz), 7.61−7.19 (m, 8H, ArH), 8.08 (m, 2H, ArH); ^{13}C NMR δ 27.51 (d, CH_2, J_{PC} 12.5 Hz),

(44) Sheldrick, G. M. *SHELXL-97, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.

(45) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham (Present distributor, Kluwer Academic Publishers: Dordrecht), 1974; Vol.IV.

(46) Spek, A. L. In *Computational Crystallography*; Sayre, D., Ed.; Clerendon Press: Oxford, 1982; p 528.

(47) Nardelli, M. *Comput. Chem.* **1983**, *7*, 95.

30.84 (d, CH_3, J_{PC} 3.2 Hz), 45.63 (d, CH, J_{PC} 14.8 Hz), 57.14 (d, C, J_{PC} 1.4 Hz), 67.03 (d, CH, J_{PC} 12.0 Hz), 122.47 (d, HC=, J_{PC} 6.9 Hz), 125.11 (d, HC=, J_{PC} 1.4 Hz), 131.17−126.11 (8 CAr), 131.40 (d, CAr, J_{PC} 10.2 Hz), 133.34 (d, HC=, J_{PC} 9.7 Hz), 133.70 (d, C=, J_{PC} 120.7 Hz), 137.38 (d, C_{ipso}, J_{PC} 132.7 Hz), 143.91 (d, C_{ipso}, J_{PC} 9.7 Hz); ^{31}P NMR δ 32.17; MS (API-ES) *m/e* 364 (M + 1, 43), 363 (M^+, 25), 362 (M − 1, 100), 306 (24). Anal. Calcd (%) for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.85. Found: C, 76.31; H, 7.19; N, 3.81.

(2*S*$_P$R**$_P$,3*SR*,8*RS*,9*SR*)-2,3,4,9-Tetrahydro-*N*-methyl-3-phenylbenzo[c]-1-aza-2λ^5-phosphole 2-oxide (14a):** yield after chromatography (ethyl acetate:hexane 4:1) 42% (0.084 g, protonation with **A8**); oil; ^{1}H NMR δ 2.46 (d, 3H, J_{PH} 8.8 Hz), 2.79 (m, 1H), 3.00 (m, 1H), 4.28 (d, 1H, *J* 9.9 Hz), 5.82 (m, 1H), 6.04−5.88 (m, 3H), 7.61−7.31 (m, 8H, ArH), 8.01 (m, 2H, ArH); ^{13}C NMR δ 28.86 (d, CH_3, J_{PC} 2.3 Hz), 42.88 (d, CH, J_{PC} 92.5 Hz), 46.19 (d, CH, J_{PC} 2.3 Hz), 67.34 (d, CH, J_{PC} 8.3 Hz), 122.51 (HC=), 126.31 (d, HC=, J_{PC} 10.6 Hz), 127.31 (d, HC=, J_{PC} 6.5 Hz), 127.76 (HC=), 132.36−128.19 (10CAr), 131.95 (d, C_{ipso}, J_{PC} 125.8 Hz), 138.07 (d, C_{ipso}, J_{PC} 7.9 Hz); ^{31}P NMR δ 43.10; MS (API-ES) *m/e* 321 (M^+, 54), 243 (41), 149 (100), 84 (45), 49 (51), 40 (71). Anal. Calcd (%) for $C_{20}H_{20}NOP$: C, 74.75; H, 6.27; N, 4.36. Found: C, 74.82; H, 6.31; N, 4.12.

(2*S*$_P$R**$_P$,3*SR*,8*RS*,9*SR*)-2,3,4,9-Tetrahydro-*N*-*tert*-butyl-3-phenylbenzo[c]-1-aza-2λ5-phosphole 2-oxide (14c):** yield after chromatography (ethyl acetate:hexane 1:1) 21% (0.043 g, protonation with **A8**); oil; ^{1}H NMR δ 1.21 (9H), 2.66 (m, 1H, *J* 21.3, *J* 10.3 Hz), 2.86 (ddt, 1H, *J* 21.3, J_{PH} 22.7, *J* 2.2 Hz), 4.51 (d, 1H, *J* 9.5 Hz), 5.61 (m, 1H,, *J* 10.3 Hz), 5.98−5.82 (m, 3H), 7.77−7.04 (m, 8H, ArH), 8.12 (m, 2H, ArH); ^{13}C NMR δ 30.96 (d, CH_3, J_{PC} 3.2 Hz), 43.28 (d, CH, J_{PC} 92.5 Hz), 44.88 (d, CH, J_{PC} 3.2 Hz), 57.03 (d, C, J_{PC} 0.9 Hz), 64.77 (d, CH, J_{PC} 8.3 Hz), 122.64 (HC=), 126.06 (d, HC=, J_{PC} 13.8 Hz), 126.26 (d, HC=, J_{PC} 8.8 Hz), 127.53 (d, HC=, J_{PC} 11.6 Hz), 132.93−127.80 (8CAr), 132.24 (d, CAr, J_{PC} 9.7 Hz), 135.08 (d, C_{ipso}, J_{PC} 124.8 Hz), 142.90 (d, C_{ipso}, J_{PC} 8.8 Hz); ^{31}P NMR δ 45.15; MS (API-ES) *m/e* 363 (M^+, 26), 362 (M-1, 100), 308 (22). Anal. Calcd (%) for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.85. Found: C, 76.14; H, 7.17; N, 3.72.

(2*S*$_P$R**$_P$,3*SR*,8*RS*,9*RS*)-2,3,4,9-Tetrahydro-*N*-*tert*-butyl-3-phenylbenzo[c]-1-aza-2λ5-phosphole 2-oxide (15c):** yield after chromatography (ethyl acetate:hexane 1:1) 4% (0.009 g, protonation with **A1**); oil; ^{1}H NMR δ 1.16 (9H), 3.24 (m, 1H, J_{PH} 21.5, *J* 21.6 Hz), 3.46 (m, 1H), 4.86 (dd, 1H, J_{PH} 16.3, *J* 6.7 Hz), 5.56 (m, 2H), 5.72 (m, 2H), 7.58−7.04 (m, 8H, ArH), 7.98 (m, 2H, ArH); ^{13}C NMR δ 30.42 (d, CH_3, J_{PC} 2.9 Hz), 37.76 (d, CH, J_{PC} 98.4 Hz), 43.97 (d, CH, J_{PC} 4.1 Hz), 55.38 (d, C, J_{PC} 2.9 Hz), 62.37 (d, CH, J_{PC} 9.5 Hz), 122.99 (HC=), 125.67 (d, HC=, J_{PC} 1.6 Hz), 126.34 (d, HC=, J_{PC} 12.0 Hz), 127.02 (d, HC=, J_{PC} 1.4 Hz), 132.42−127.57 (8CAr), 132.86 (d, CAr, J_{PC} 9.5 Hz), 134.78 (d, C_{ipso}, J_{PC} 119.3 Hz), 141.47 (C_{ipso}); ^{31}P NMR δ 40.07; MS (API-ES) *m/e* 364 (M + 1, 20), 256 (100). Anal. Calcd (%) for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.85. Found: C, 76.00; H, 7.25; N, 3.68.

(2*S*$_P$R**$_P$,8*RS*,9*RS*)-2,3,4,7-Tetrahydro-*N*-*tert*-butyl-3-phenylbenzo[c]-1-aza-2λ^5-phosphole 2-oxide (16c):** yield after chromatography (ethyl acetate:hexane 1:1) 17% (0.033 g, protonation with **A1**); mp 208−209 °C;^{1}H NMR δ 1.13 (s, 9H), 2.59 (m, 2H), 3.87 (m, 1H), 4.88 (dd, 1H, J_{PH} 7.7, *J* 18.0 Hz), 5.31 (m, 1H, *J* 10.3 Hz), 5.43 (m, 1H), 6.58 (m, 1H, J_{PH} 16.1 Hz), 7.56−7.11 (m, 8H, ArH), 7.97 (m, 2H, ArH); ^{13}C NMR δ 26.85 (d, CH_2, J_{PC} 12.4 Hz), 30.56 (d, CH_3, J_{PC} 2.5 Hz), 42.49 (d, CH, J_{PC} 16.1 Hz), 55.38 (d, C, J_{PC} 2.9 Hz), 64.04 (d, CH, J_{PC} 12.0 Hz), 123.47 (d, HC=, J_{PC} 6.6 Hz), 124.30 (HC=), 132.19−126.34 (8CAr), 131.57 (d, CAr, J_{PC} 10.8 Hz), 133.03 (d, C=, J_{PC} 126.5 Hz), 134.61 (d, HC=, J_{PC} 9.9 Hz), 137.15 (d, C_{ipso}, J_{PC} 128.6 Hz), 142.20 (C_{ipso}); ^{31}P NMR δ 26.20. MS (API-ES) *m/e* 365 (M + 2, 20), 364 (M + 1, 100), 308 (15). Anal. Calcd (%) for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.85. Found: C, 76.08; H, 7.15; N, 3.88.

General Procedure for the Preparation of λ-*N*-Methylaminophosphinic Acids 21 and 22. To a solution of the appropriate phosphole (**7**, **9**) (0.45 × 10^{-3} mol) in acetone (10 mL) was added 2 N HCl (1 mL) at room temperature, and the mixture was stirred for 30 min. Then, the pH was set to neutral by adding 1 N NaOH and the reaction was extracted with ethyl acetate (3 × 15 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo, affording a white solid that was washed with diethyl ether. Aminophosphinic acid **21a** has been characterized previously.[21]

(1*SR*,6*RS*,7*SR*)-1-[6-(Benzylamino)benzyl)-2,4-cyclohexadienyl]phenylphosphinic acid (21b): yield 96% (0.192 g); mp 218−219 °C; ^{1}H NMR δ 2.26 (d, 1H, *J* 22.8 Hz), 2.47 (dddd, 1H, J_{PH} 2.7, *J* 22.8, *J* 7.9 Hz), 3.53 (d, 1H, *J* 13.9 Hz), 3.54 (m, 1H), 4.33 (d, 1H, *J* 13.9), 4.38 (m, 1H), 5.22 (m, 1H), 5.55 (dd, 1H, *J* 9.7, *J* 4.0 Hz), 5.93 (dd, 1H, J_{PH} 19.7, *J* 4.0 Hz), 7.60−7.11 (m, 13H, ArH), 7.97 (m, 2H, ArH), 12.13 (bs, OH + NH); ^{13}C NMR δ 26.94 (d, CH_2, J_{PC} 13.6 Hz), 38.61 (d, CH, J_{PC} 9.1 Hz), 48.21 (CH_2), 65.62 (CH), 125.75 (HC=), 127.19 (HC), 130.70−127.74 (13CAr), 131.64 (C_{ipso}), 132.71 (d, CAr, J_{PC} 9.1 Hz), 134.17 (C_{ipso}), 134.92 (d, C_{ipso}, J_{PC} 137.3 Hz), 136.92 (HC=), 138.21 (d, C=, J_{PC} 128.6 Hz); ^{31}P NMR δ 26.40; MS (API-ES) *m/e* 417 (M + 2, 30), 416 (M + 1, 100), 309 (15), 241 (10). Anal. Calcd (%) for $C_{26}H_{26}NO_2P$: C, 75.16; H, 6.31; N, 3.37. Found: C, 75.15; H, 6.24; N, 3.33.

(1*SR*,6*RS*,7*SR*)-1-[6-(tert-Butylamino)benzyl)-2,4-cyclohexadienyl]phenylphosphinic acid (21c): yield 97% (0.194 g); mp 220−221 °C; ^{1}H NMR δ 1.26 (s, 9H), 2.57 (s, 1H), 3.72 (d, 1H, *J* 9.1 Hz), 4.57 (m, 1H), 5.09 (m, 1H), 5.54 (d, 1H, *J* 9.1 Hz), 5.86 (d, 1H, J_{PH} 19.8 Hz), 7.58−6.99 (m, 8H, ArH), 8.00 (m, 2H, ArH), 10.59 (bs, OH), 13.00 (bs, NH); ^{13}C NMR δ 27.04 (CH), 27.26 (CH_3), 39.15 (d, CH, J_{PC} 9.3 Hz), 56.65 (C), 65.04 (CH), 125.18 (HC=), 130.11−127.52 (8CAr), 128.56 (d, HC=, J_{PC} 6.5 Hz), 132.92 (d, CAr, J_{PC} 8.6 Hz), 133.98 (d, HC=, J_{PC} 12.4 Hz), 136.56 (d, C_{ipso}, J_{PC} 133.3 Hz), 137.90 (C_{ipso}), 141.55 (d, C=, J_{PC} 122.3 Hz); ^{31}P NMR δ 24.57; MS (API-ES) *m/e* 383 (M + 2, 25), 382 (M + 1, 100). Anal. Calcd (%) for $C_{23}H_{28}NO_2P$: C, 72.42; H, 7.40; N, 3.67. Found: C, 72.32; H, 7.45; N, 3.67.

(6*RS*,7*SR*)-1-[6-(Methylamino)benzyl)-1,4-cyclohexadienyl]phenylphosphinic acid (22a): yield 97% (0.194 g); mp 129−130 °C dec; ^{1}H NMR δ 2.39 (s, 3H), 2.53 (m, 2H), 3.63 (d, 1H, *J* 8.3 Hz), 4.30 (m, 1H, *J* 8.2, *J* 4.7 Hz), 5.26 (m, 1H), 5.62 (m, 1H), 6.04 (d, 1H, J_{PH} 19.5 Hz), 7.61−7.16 (m, 8H, ArH), 7.67 (m, 2H, ArH), 10.88 (bs, OH), 12.78 (bs, NH); ^{13}C NMR δ 27.02 (d, CH_2, J_{PC} 13.2 Hz), 31.28 (CH_3), 38.86 (d, CH, J_{PC} 9.1 Hz), 70.21 (CH), 125.94 (HC=), 126.67 (d, HC=, J_{PC} 6.6 Hz), 130.64−127.75 (8CAr), 134.20 (C_{ipso}), 135.31 (d, C_{ipso}, J_{PC} 136.0 Hz), 136.69 (d, HC=, J_{PC} 11.6 Hz), 138.25 (d, C=, J_{PC} 124.5 Hz); ^{31}P NMR δ 28.03. MS (API-ES) *m/e* 341 (M + 2, 22), 340 (M + 1, 100), 309 (8). Anal. Calcd (%) for $C_{20}H_{22}NO_2P$: C, 70.78; H, 6.53; N, 4.13. Found: C, 70.73; H, 6.46; N, 4.12.

(6*RS*,7*SR*)-1-[6-(Benzylamino)benzyl)-1,4-cyclohexadienyl]phenylphosphinic acid (22b): yield 91% (0.182 g); mp 228−229 °C; ^{1}H NMR δ 2.73 (d, 1H, J_{PH} 19.8 Hz), 3.52 (m, 1H), 3.60 (d, 1H, *J* 13.0 Hz), 3.91 (d, 1H, *J* 13.0 Hz), 4.17 (d, 1H, *J* 10.2 Hz), 4.98 (m, 1H, *J* 15.2, *J* 6.8 Hz), 5.63 (dd, 1H, *J* 9.6, *J* 4.5 Hz), 5.69 (ddd, 1H, J_{PH} 11.9, *J* 8.8, *J* 2.8 Hz), 5.88 (m, *J* 8.8, *J* 3.9 Hz), 7.56−7.13 (m, 13H, ArH), 7.90 (m, 2H, ArH), 11.72 (bs, OH), 12.71 (bs, NH); ^{13}C NMR δ 35.13 (CH), 41.45 (d, CH, J_{PC} 95.4 Hz), 48.88 (CH_2), 57.63 (CH), 123.85 (HC=), 125.03 (HC=), 125.63 (d, HC=, J_{PC} 11.1 Hz), 129.47−127.65 (13CAr), 128.82 (d, HC=, J_{PC} 12.5 Hz), 132.22 (C_{ipso}), 132.28 (d, CAr, J_{PC} 8.7 Hz), 135.32 (C_{ipso}), 136.13 (d, C_{ipso}, J_{PC} 127.3 Hz); ^{31}P NMR δ 29.38; MS (API-ES) *m/e* 417 (M + 2, 30), 416 (M + 1, 100), 398 (10). Anal. Calcd (%) for $C_{26}H_{26}NO_2P$: C, 75.16; H, 6.31; N, 3.37. Found: C, 75.13; H, 6.39; N, 3.27.

(6*RS*,7*SR*)-1-[6-(tert-Butylamino)benzyl)-1,4-cyclohexadienyl]phenylphosphinic acid (22c): yield 94% (0.188 g); mp 219−224 °C dec; ^{1}H NMR δ 1.28 (s, 9H), 3.62 (ddd, 1H, J_{PH} 23.9, *J* 7.5, *J* 6.4 Hz), 3.84 (ddd, 1H, J_{PH} 34.4, *J* 11.5, *J* 7.5 Hz), 4.47 (t, 1H, *J* 10.0 Hz), 4.61 (dd, 1H, *J* 9.5, *J* 2.5 Hz), 5.28 (m, 1H), 5.93 (m, 1H, *J* 9.3, *J* 4.9 Hz), 6.24 (m, 1H), 7.55−7.28 (m, 8H, ArH), 7.90 (m, 2H, ArH), 10.10 (bs, OH), 11.31 (bs, NH); ^{13}C NMR δ 27.14 (CH_3), 40.25 (CH), 41.02 (d, CH, J_{PC} 82.2 Hz), 58.67 (C), 60.46 (CH), 123.59 (HC=), 124.62 (d,

HC═, J_{PC} 4.0 Hz), 125.37 (d, HC═, J_{PC} 10.6 Hz), 125.53 (d, HC═, J_{PC} 8.1 Hz), 131.30−127.47 (8CAr), 132.29 (d, CAr, J_{PC} 9.5 Hz), 133.23 (d, C═, J_{PC} 130.2 Hz), 135.44 (C_{ipso}); ^{31}P NMR δ 28.66; MS (API-ES) *m*/*e* 383 (M + 2, 25), 381 (M + 1, 100). Anal. Calcd (%) for $C_{23}H_{28}NO_2P$: C, 72.42; H, 7.40; N, 3.67. Found: C, 72.43; H, 7.39; N, 3.63.

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Supporting Information Available: Figure S1, distribution of products for the protonation with *p*-toluensulfonic acid; Figures S2 and S3, 1D gNOESY spectra of **7b** and **9b**, respectively; Table S1, distribution of products in the dearomatization−protonation reactions of **6b** using HMPA as cosolvent, characterization of **19** and **20**, and X-ray data of **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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