Tuning the anionic cyclization-protonation of *N*-benzyl(diphenyl)-phosphinamides. Highly efficient synthesis of tetrahydrobenzo-1-aza-2λ^5-phospholes containing a 1,3-cyclohexadiene system

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Dedicated to Prof. J. Elguero and Prof. P. Molina on the occasion of their 70th and 65th birthdays, respectively

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Abstract

A study of the dearomatization of *N*-alkyl-*N*-benzyldiphenylphosphinamides through anionic cyclization followed by protonation with a wide range of protonating reagents has been carried out. The proton sources used include alcohols, phenols, amines, amides, and organic acids. The effect of the *N*-alkyl substituent, the acidity, and the size of the protonating reagent were analyzed. The mixtures of products formed were derived predominantly from α– and γ–protonation with respect to the phosphorus. Addition of *tert*-butyldimethylsilyl chloride to the reaction medium prior to the protonation with methanol allowed the preparation of tetrahydrobenzo-[c]-1-aza-2λ^5-phospholes containing a 1,3-cyclohexadiene with a *cis*-fusion of the rings in very high yields.

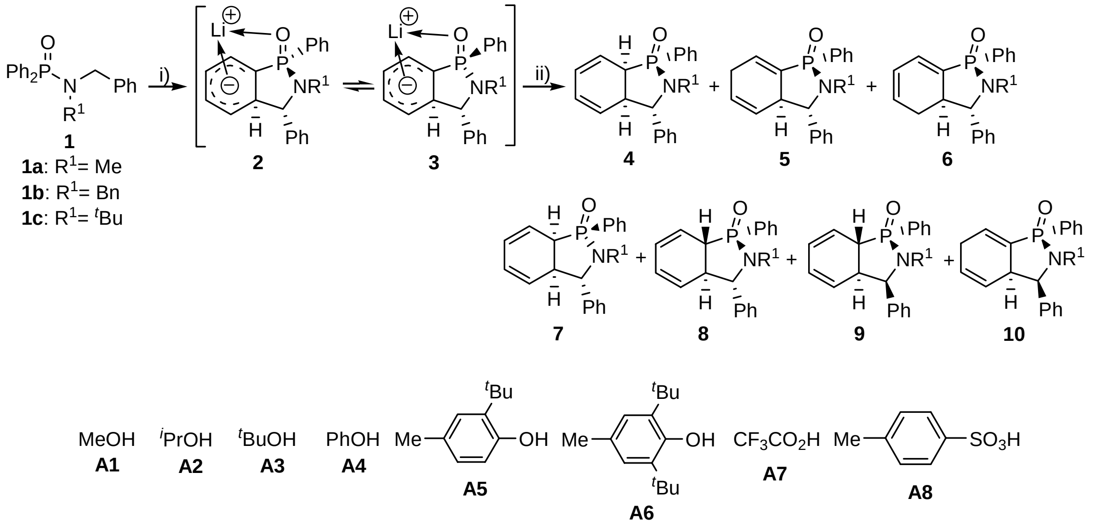
Keywords: Phosphinamides, dearomatization, anionic cyclization, [1,3]-cyclohexadienes, protonation, azaphospholes

Introduction

Dearomatizing reactions through anionic cyclization and subsequent electrophilic quenching represent an attractive approach to the preparation of functionalized alicyclic compounds, and have received great attention in the last five years.[1]

Anionic cyclization onto an unactivated aromatic ring generally leads to aromatized products, owing to the harsh reaction conditions used and/or the absence of electron-withdrawing substituents in the ring capable of stabilizing the intermediate dearomatized metallated species.[2] Stable dearomatized compounds are obtained when the anionic cyclization–electrophilic trapping sequence of reactions is performed onto aromatic rings bearing Michael acceptors such as sulfone,[2] sulfonamide,[3] carboxamide,[4] nd triazene.[2] Generally, this dearomatization methodology affords functionalized dihydrobenzene and dihydronaphthalene derivatives with high degrees of chemo-, regio-, and stereocontrol which, in the particular case of arylcarboxamides, have been used as precursors in the synthesis of natural products [2] and non-natural analogues.[2]

With regard to organophosphorus compounds, Schlosser and Schaub used NMR to characterize the dearomatized anion resulting from the intramolecular attack of an *ortho*-lithiated phenyl ring of triphenylmethylenephosphorane to the *ortho-* position of an adjacent *P*-phenyl substituent.[1] The anion aromatized through loss of benzene to give *P*-methyldibenzophosphole. We have recently reported the dearomatization of a phenyl[1] and naphthyl[1] ring linked to the phosphorus atom of *N*-alkyl-*N*-benzyldiphenylphosphinamide **1** by treatment with s-BuLi in the presence of HMPA or DMPU at –90 ºC in THF (Scheme 1). The dearomatized phosphorus-stabilized anions formed in the anionic cyclization[1] were protonated[2] or reacted with alkyl halides and aldehydes to afford tetrahydrobenzo[*c*][1,2]aza-1λ^5-phospholes with moderate to excellent regio- and stereocontrol.[3] These heterocycles were further transformed into γ-aminophosphinic acids and methyl esters,[10,11,13,14] an important class of compounds, owing to their activity as enzyme inhibitors,[4] and on GABA receptors.[5]



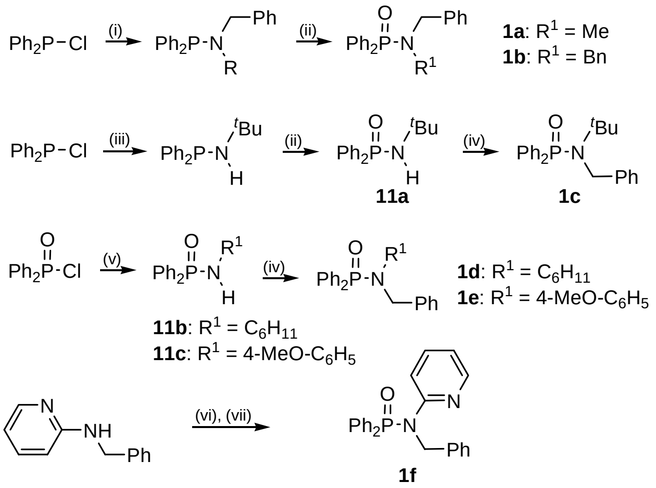
Scheme 1. (i) s-BuLi (1.5 equiv.), THF –90 ºC, HMPA (6 equiv.), 30 min. (ii) **A1**-**A8**, –90 ºC, THF, 30 min (for **A8**: 12 h).

Protonation of the dearomatized anions **2,3** might take place at the α-, γ-, and ε- positions with respect to the phosphorus. Our previous study on the anionic cyclization of **1a–c** and subsequent protonation with the acids **A1**–**A8** (Scheme 1) showed that 2,6-di-(*tert*-butyl)-4-methylphenol protonates exclusively at the γ position.[13] In this way, the heterocycles **5a–c** containing a 1,4-cyclohexadiene substructure could be prepared in almost quantitative yields. In contrast, products **6** arising from ε-protonation were formed only as by-products when the proton source used was methanol (yields lower than 5%). This weak acid proved to be the best choice for protonating at the position α- to the phosphorus, leading to tetrahydrobenzoazaphospholes **4** in yields ranging from 28% to 65%.

Although γ-protonation of the anionic species **2,3** can be achieved with total regioselectivity, the synthesis of azaphospholes **4** was clearly less efficient. In order to improve the synthetic utility of the anionic cyclization-protonation reaction of *N*-benzyldiphenylphosphinamides **1** we have undertaken a study in which the influence of a wide range of proton sources has been investigated with the aim of favoring the regioselective formation of heterocycles **4** having a [1,3]- cyclohexadiene system. The effect of the substituent on the nitrogen of the phosphinamide has been also evaluated in terms both of bulkiness and electronic properties. The results of this work are reported here. We have found that exclusive protonation α- to the phosphorus can be achieved with methanol when the dearomatized anions are treated with *tert*-butyldimethylsilyl chloride prior to the quench with the protonating reagent.

Results and Discussion

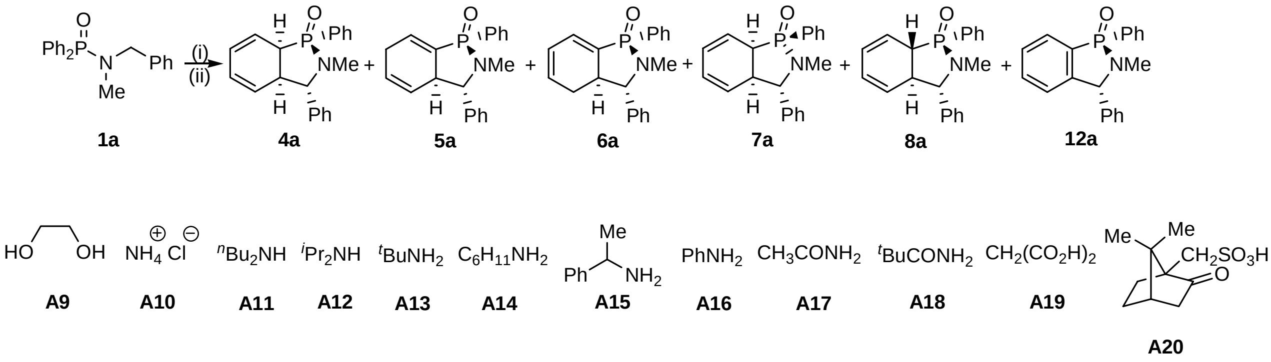
The phosphinamides **1a–c** (**a**: R^1= Me, **b**: R^1= Bn, **c**: R^1= t-Bu) were prepared according to the methods previously described (Scheme 2).[13] Phosphinamides **1d,e** (**d**, R^1= C_6H_{11}: **e**, R^1= *p*-MeO-C_6H_4) were more efficiently synthesized by adding the appropriate commercial amine to a toluene solution of chlorodiphenylphosphine oxide and triethylamine. The resulting *N*-cyclohexyldiphenylphosphinamide[5] **11b** and *N*-(4-methoxyphenyl)diphenylphosphinamide[7] **11c** were benzylated by addition of benzyl bromide to the sodium amide formed upon treatment of **11b–c** with sodium hydride (Scheme 2).[7] The synthesis of phosphinamide **1f** (R^1= 2-Py) was performed by reaction of lithium 2-benzylaminopyridine, obtained by treating the corresponding amine with n-BuLi, with chlorodiphenylphosphine oxide in THF at –78 ºC.



Scheme 2. (i) $BnNHR^1$ (R^1 = Me, Bn), Et_3N (2.5 equiv.), toluene, 30 min, -78 ºC. (ii) 30% H_2O_2/THF, 30 min. (iii) t-$BuNH_2$, Et_3N (2.5 equiv.), toluene, 30 min, -78 ºC. (iv) NaH, THF, 30 min, 0 ºC, then $PhCH_2Br$, 60 min, r.t. (v) R^1NH_2 (R^1 = C_6H_{11}, 4-MeO-C_6H_4), Et_3N (2.5 equiv.), toluene, 60 min, –78 ºC. (vi) n-BuLi (1 equiv.), THF, -30 ºC, 15 min. (vii) $Ph_2P(O)Cl$ (1 equiv.), –78 ºC, 1h.

Dearomatization–protonation studies

The standard conditions for the anionic dearomatization–protonation process consisted in the metalation of **1** with 2.5 equivalents of s-BuLi at –90ºC during 30 min in the presence of HMPA (6 equiv.) followed by addition at the same temperature of a solution of the appropriate proton source in THF, via cannula. The reaction mixture was stirred for 30 min. and then processed through conventional aqueous workup. When the solubility of the protonating reagent under the reaction conditions essayed was very small the time for quenching was increased to 12 h. As in our previous study, we used the phosphinamide **1a** as reference for evaluating the effect of the selected protonating reagents on the regio- and diastereoselectivity ratios. The acids used are shown in Scheme 3. They include the diol **A9**, ammonium chloride **A10**, a series of aliphatic primary and secondary amines **A11**–**A15**, aniline **A16**, two amides **A17** and **A18**, and two organic acids **A19** and **A20**. They cover a broad range of pK_a values and the large variation of the bulkiness of the substituents on the nitrogen might contribute to reveal possible steric effects.[5] The products obtained are given in Scheme 3, and their distribution as a function of the quenching reagent used is collected in Table 1. To make the comparison easier, the data corresponding to the protonation with methanol **A1**, the hindered phenol **A6**, and the sulfonic acid **A8** (Scheme 1) are also included. These acids are the best quenching reagents for the synthesis of heterocycles **4a**, **5a**, and **8a**, respectively (entries 1–3).



Scheme 3. (i) s-BuLi (1.5 equiv.), THF –90 ºC, HMPA (6 equiv.), 30 min. (ii) **A9**–**A20**, –90 ºC, THF, 30 min. (12 h for **A17**, **A18**).

Table 1. Distribution of products (in %) formed in the anionic cyclization of 1a and protonation with acids A1, A6, A9–A20

		Ratio							
Entry	Acid	**4a**	**5a**	**6a**	**7a**	**8a**	Yield	α:γ	**12a**
1	**A1**[a]	72	20	3	5		90	79:21	
2	**A6**[a]		100				98	<1:99	
3	**A8**[a]	16	24	2	8	50	84	76:24	
4	**A9**	22	50	8	5	15	80	34:66	
5	**A10**	32	48	11	9		44	46:54	
6	**A10**[b]	27	51	12	10		56	42:58	
7	**A11**	64	31	1	4		90	69:31	7
8	**A12**	40	36	7	4	13	80	61:39	7
9	**A13**	18	56	16	10		79	33:67	12
10	**A14**	21	67	8	4		90	27:73	6
11	**A15**	53	34	10	3		83	62:38	8
12	**A16**	35	35	5	6	19	87	63:37	3
13	**A17**[b]	85	9		6		81	91:9	
14	**A18**	65	25	4	6		61	74:26	
15	**A18**[b]	67	25	2	6		85	75:25	
16	**A19**	17	51		3	29	87	49:51	
17	**A20**	18	48		2	32	88	52:48	

[a] Data taken from reference 13. [b] Protonation during 12 h.

The compounds **4a**–**8a** and **12a** have been characterized previously.[10,13] Protonation with the dihydroxylic alcohol **A9** proved to be detrimental for the regio- and diastereoselectivity of the reaction, as compared with the other oxygen acids **A1** and **A6** (*c.f.*, entries 1, 2, and 4). Any possible chelating effect produced by **A9** contributes to the indiscriminate protonation of the anionic species formed in the nucleophilic dearomatization. Trapping reactions with primary and secondary amines were also disappointing. Mixtures of dearomatized products corresponding to α-, γ-, and ε- protonation were obtained with low regioselectivity and diastereomeric ratios. Furthermore, in all cases a small amount of the aromatized compound **12a** was also formed (yield of 3% to 12%, entries 7–12). Increasing the acidity seems to favor the formation of tetrahydrobenzoazafosfol **8a** (entry 12). However, quenching the reaction with ammonium chloride **A10** produced a marked reduction in the conversion without a significant improvement in the regioselectivity (entry 5). The yield increased slightly when the time for protonating is prolonged to 12 h (entry 6).

The use of stronger acids such as **A19** and **A20** led to a distribution of products that follows the trend observed in the protonations with **A1** and **A8**: the regioselectivity of the reaction is low and the amount of regioisomer **8a** obtained increases notably (entries 16,17). Fortunately, better results were obtained when acetamide, **A17**, was used as proton source (entry 13). The quenching with **A17** afforded the highest ratio of α:γ regioisomers (91:9) and also the highest stereoselectivity in the formation of benzoazaphosphole **4a** of all the acids tried. Additionally, the yield of **4a** increased (13%) compared to the protonation with methanol **A1**. The use of the bulkiest amide **A18** for the protonation produced a remarkable decrease of yield and the α:γ ratio. Extending the protonation time to 12 h resulted in an increase in the yield to 85% (entry 15) without affecting the regio- and stereoselectivity of the reaction.

The improved conditions for the preparation of **4a** were applied to the analogous reaction with the phosphinamides **1b**,**c**. On the other hand, the anionic dearomatizing cyclization–protonation method was also extended to phosphinamides **1d–f**. With these starting materials the acids **A1**, **A6** and **A8** most suitable for the respective synthesis of heterocycles **4**, **5**, and **8**, were also investigated. The results obtained are given in Table 2.

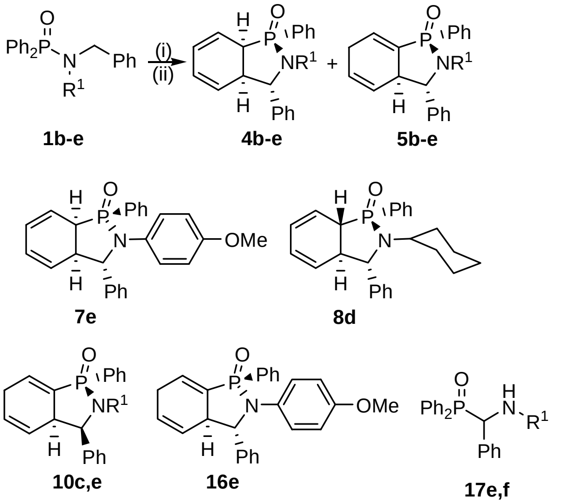
Protonation of the dearomatized anions of phosphinamides **1b–d** with acetamide **A17** proved to be less selective than for anions derived from **1a** (Scheme 4). The ratios of α:γ protonated products ranged from 71:29 to 40:60. As for **1a**, higher yields were obtained when the time for protonation increased from the 30 min used in the standard reaction conditions to 12 h (entries 9,10). Not unexpectedly, the lowest yield was observed for phosphinamide **1c** bearing the bulky *tert*-butyl group on the nitrogen.

As noted previously[13] for **1b** the use of an excess of base and HMPA led to the formation of by-products **13** and **14** by virtue of the metalation of the benzyl substituent of **4b** and **5b**, respectively, and subsequent addition of the new anions to the *N*-methylmethyleneimine **15** resulting from the deprotonation of the HMPA (Scheme 5).[21]

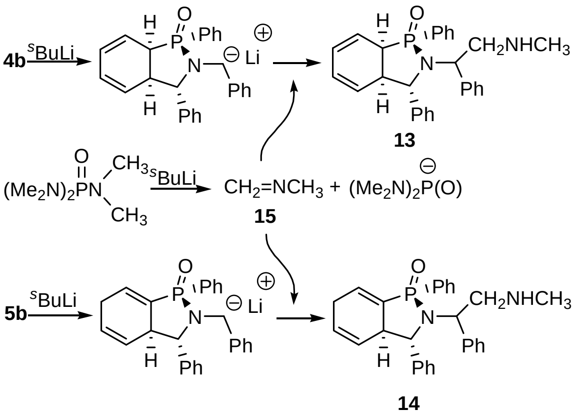
Table 2. Distribution of products (in %) formed in the anionic cyclization-protonation of **1b**–**f**

			Ratio										
Entry	**1**	Acid	**4**^{a}	**5**^{a}	**7**^{a}	**8**^{a}	**10**	**13**	**14**	**16**	Yield	α:γ	**17**
1	b	**A17**^{b}	52(b)	25(b)				14	9		87	68:32	
2	b	**A17**^{b,c}	60(b)	40(b)							84	60:40	
3	c	**A17**^{b}	71(c)	16(c)			13(c)				70	71:29	
4	d	**A1**	50(d)	50(d)							85	50:50	
5	d	**A6**		100(d)							67	<1:99	
6	d	**A6**^{d}		100(d)							98	<1:99	
7	d	**A8**	10(d)	50(d)		40(d)					67	50:50	
8	d	**A8**^{b}	12(d)	44(d)		44(d)					82	56:44	
9	d	**A17**	40(d)	60(d)							87	40:60	
10	d	**A17**^{b}	43(d)	57(d)							98	43:57	
11	e	**A1**	59(e)	16(e)	14(e)		11(e)				52^{e}	71:29	3(e)
12	e	**A6**		69(e)			15(e)			16(e)	58^{e}	<1:99	17(e)
13	f	**A1**									-	-	>98(f)

[a] b: R^1= Bn, c: R^1= t-Bu, d: R^1= C_6H_{11}, e: R^1= *p*-MeO-C_6H_4, f: R^1= 2-Py. [b] Protonation during 12 h. [c] The cosolvent used was DMPU. [d] The metalation was performed during 12 h. [e] 9% of $Ph_2P(O)$-s-Bu was also isolated. [f] 26 % of $Ph_2P(O)H$ was also obtained. [g] 12% of $Ph_2P(O)H$ was also obtained.



Scheme 4. (i) *s*-BuLi (1.5 equiv.), THF –90 ºC, HMPA (6 equiv.), 30 min. (ii) **An**, –90 ºC, THF, 30 min to 12 h.



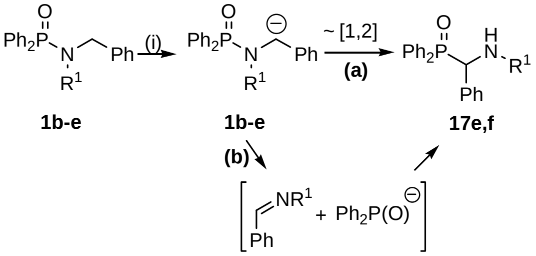
Scheme 5

Methanol **A1** and 2,6-di-(*tert*-butyl)-4-methylphenol **A6** were again the best acids for the selective preparation of tetrahydrobenzoazaphospholes **4d** and **5d** containing, respectively, a [1,3]- and a [1,4]-cyclohexadiene system. With methanol a 1:1 mixture of **4d**:**5d** was obtained, and was separated by flash-column chromatography using ethyl acetate:hexane, 1:1, as eluent. The protonation with phenol **A6** afforded exclusively **5d**. The reaction could be quantitatively improved by increasing the time for metalation from 30 min to 12 h (*cf*., entries 5 and 6). With *p*-toluenesulfonic acid, **A8**, as proton source the regioselectivity of the reaction decreased notably. As with **1a–c**, this protonating reagent produced the highest yield of regioisomer **8d** (entries 7, 8).

The new products obtained were easily identified by comparing their ^{1}H-, ^{1}H{^{31}P}-, and ^{13}C-NMR spectra with those of the same series of compounds previously characterized. 1,4-Cyclohexadiene derivatives were characterized by the large deshielding ($\delta > 6.2$ ppm) and large coupling with the phosphorus ($^{3}J_{PH} > 16$ Hz) of the C_{β}–H to the phosphorus. For compounds having a 1,3-cyclohexadiene moiety the olefinic protons were observed at $\delta < 6.5$ ppm and the methine carbon linked to the phosphorus ($\delta < 45$ ppm) appeared as a doublet of $^{1}J_{PC} > 75$ Hz in the ^{13}C- NMR spectra. The *trans*- junction of the bicyclic system of **8d** was deduced from the large vicinal coupling between the bridgehead protons, $^{3}J_{HH}^{trans} = 20.6$ Hz. Epimerization of the methine carbon linked to the nitrogen of **5** and **10** was revealed by the appearance of a $^{3}J_{PH}$-coupling in the proton spectrum of **10**. In all cases, the relative configurations assigned were confirmed through NOE measurements.

The use of the phosphinamide **1e** as starting material, bearing a *p*-methoxyphenyl group on the nitrogen instead of the *N*-alkyl substituent of phosphinamides **1a–d** resulted in a rather inefficient dearomatization–protonation process. Low yields, and regio- and stereo-selectivities were obtained with acids **A1** and **A6** (entries 11,12). Besides the products **4–10** already described in the series of phosphinamides **1a–d**, a new γ-protonated stereoisomer **16** was isolated, in 16% yield. The appearance in the proton spectrum of the signal of the C_{β}-H to the phosphorus at $\delta = 6.23$ ppm with a $^{3}J_{PH}$ coupling of 17.6 Hz established that it is a γ-protonated derivative. The inversion of the configuration of the phosphorus with respect to **5d** was confirmed by the NOE observed on the *ortho* protons of the *P*-phenyl ring upon selective inversion of the methine proton adjacent to the nitrogen atom. Furthermore, a non-dearomatized product **17** was isolated in significant amounts in the protonation with phenol **A6** (17%, entry 12). The ^{1}H- and ^{13}C-NMR spectra of compound **17** were very simple. In the ^{13}C- spectrum, the methine carbon linked to the nitrogen and phosphorus atoms appeared as a doublet at $\delta = 53.5$ ppm with $^1J_{PC} = 76.9$ Hz. The formation of **17** may be explained through the evolution of the benzylic anion generated in the metallation of **1e** via two mechanisms competing with the anionic cyclization: (a) a [1,2]-rearrangement,[22] or (b) a β-elimination of the diphenylphosphinoyl group followed by addition to the resulting imine intermediate.[21] The identification of diphenylphosphine oxide in the crude reaction mixture after workup is consistent with mechanism (b), although the participation of the alternative pathway (a) can not be completely discarded (Scheme 6). Owing to the disappointing results obtained with phosphinamide **1e** no further studies with other proton sources were pursued.

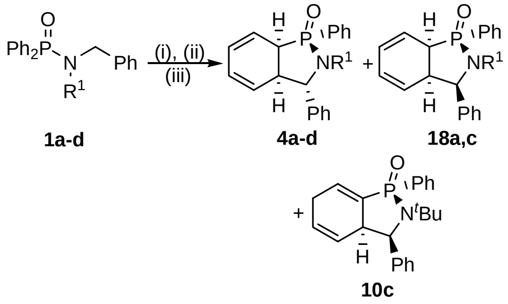
Finally, the dearomatization–protonation process was studied with the phosphinamide **1f**. Unfortunately, upon lithiation of **1f** with *s*-BuLi in THF, either in the presence of HMPA and DMPU or without cosolvents, only the rearranged product **17f** was obtained—in quantitative yields. The 2-pyridyl substituent on the nitrogen seems to accelerate the rearrangement to **17f** probably through chelation of the lithium cation.



Scheme 6. i. *s*-BuLi (1.5 equiv.), THF –90 ºC, HMPA (6 equiv.), 30 min, then H_2O.

Dearomatization–silylation–protonation

The NMR study of the dearomatizing anionic cyclization of phosphinamide **1a** has shown that the lithium cation of the intermediate dearomatized anions is intramolecularly coordinated to the PO group.[12b] We reasoned that short circuiting this coordination might favor the regioselective formation of α-protonated products. To validate this hypothesis we treated the lithiated dearomatized species with *tert*-butyldimethylsilyl chloride (TBDMSCl) prior to the addition of the protonating reagent. To our delight, the three-step, one-pot process involving first lithiation of phosphinamides **1a**–**d** with 2.5 equiv. of *s*-BuLi in THF at –90 ºC in the presence of 6 equiv. of HMPA during 30 (**1a**,**b**), or 60 (**1c**,**d**) min, and then reaction with TBDMSCl (2.5 equiv.) during an extra 30 min, and finally, addition of methanol **A1** and subsequent aqueous workup afforded high yields of the α–protonated tetrahydrobenzoazaphospholes **4a**–**d** with excellent regio- and stereoselectivity (Scheme 7). The results are shown in Table 3, including those obtained without the use of silylating reagent for comparison.



Scheme 7. (i) *s*-BuLi (2.5 equiv.), THF –90 ºC, HMPA (6 equiv.), 30–60 min. (ii). TBDMSCl (2.5 equiv.), –90 ºC, THF, 30 min. (iii) methanol (**A1**), –90 ºC, THF, 30 min.

Table 3. Distribution of products (in %) formed in the anionic cyclization-silylation-methanolysis of **1a**–**d** (**a**: R^1= Me, **b**: R^1= Bn, **c**: R^1= *t*-Bu, **d**: R^1= C_6H_{11})

					Ratio							
Entry	**1**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**18**	Yield	α:γ	$Ph_2P(O)$*s*-Bu
1	**a**[a]	72(**a**)	20(**a**)	3(**a**)	5(**a**)					90	79:21	6
2	**a**	99(**a**)							1(**a**)	97	>99:1	1
3	**a**[b]	83(**a**)			7(**a**)				10(**a**)	84	>99:1	5
4	**a**[c]	28(**a**)	28(**a**)		11(**a**)	33(**a**)				53	72:28	18
5	**b**[a]	78(**b**)	22(**b**)							80	78:22	6
6	**b**	100(**b**)								84	>99:1	4
7	**c**[a]	46(**c**)	20(**c**)				7(**c**)	27(**c**)		58	54:46	
8	**c**[e]	61(**c**)						12(**c**)	27(**c**)	69	88:12	
9	**d**[a]	50(**d**)	50(**d**)							85	50:50	
10	**d**[e]	100(**d**)								81	>99:1	

[a] Products obtained without the use of TBDMSCl. [b] The co-solvent used was DMPU. [c] The silylating reagent used was Ph_2SiCl_2. [d] xxxx [e] Metallation during 1 h.

It is remarkable that the use of TBDMSCl prior to the addition of methanol to the reaction mixture completely inhibits the formation of product **5**. γ-Protonation to give **5** represented the major competing reaction in all attempts aimed toward the regioselective preparation of **4** (see Tables 1 and 2). The phosphinamides **1a**,**b**,**d** afforded almost exclusively the respective tetrahydrobenzoazaphospholes **4a**,**b**,**d** (entries 2, 6, 10). The amount of $Ph_2P(O)$*s*-Bu formed by attack of the base to the phosphorus atom on the phosphinamide was also slightly reduced (cf., entries 1,2 and 5,6). The reaction of phosphinamide **1c**, bearing the bulkiest substituent linked to the nitrogen, gave a mixture of three products **4c**:**10c**:**18c** in a ratio 61:12:27 (entry 8), which were separated by column chromatography. Compounds **10c** and **18c** are epimers of **5c** and **4c**, respectively, on the carbon adjacent to the nitrogen. It has been shown previously that the amount of **10c** obtained increases with increasing steric hindrance derived from the bulkiness of the N-R^1 group of the phosphinamide.[13] The same effect may explain the formation of the new derivative **18c** under reaction conditions that favor the protonation at the position α- to the phosphorus. As mentioned above, epimers at the *CH*-N carbon are readily distinguished by their ^{31}P,^{1}H- couplings. In compound **18c** this proton appears in the ^{1}H- NMR spectrum as a double doublet at δ= 4.73 ppm due to the coupling to the phosphorus ($^3J_{PH}$= 19.9 Hz) and the vicinal bridged proton ($^3J_{HH}$= 7.5 Hz). No ^{31}P,^{1}H- coupling can be resolved for the same proton of epimer **4c**. The assignment made was confirmed through 1-D selective NOE experiments.

In the reaction of phosphinamide **1a** negligible amounts of **18a** were also detected (entry 2). Curiously, the proportion of **18a** formed increased to 10% when the co-solvent used in the reaction was DMPU (entry 3). Generally, in the dearomatization–protonation process performed without intercalating a silylation step, better results are obtained using DMPU as coordinating agent, instead of HMPA. On the other hand, the silylation of the dearomatized anions of **1a** with Ph_2SiCl_2 proved to be highly detrimental for the reaction (entry 4). The yield decreased to 53%, the amount of side-product $Ph_2P(O)$-*s*-Bu increased significantly (18%), and the regioisomers **4a**:**5a** were obtained without any discrimination (ratio 1:1).

In summary, new examples of the dearomatizing anionic cyclization-protonation process have been studied. For phosphinamides where the N-R^1 group is an alkyl moiety, dearomatized products are obtained predominantly. However, when the group R^1 is an aromatic ring, rearranged products are obtained in significant amounts or exclusively. The study of the protonation step has been extended to a series of oxygen- and nitrogen- proton sources. 2,6-Di-(*tert*-butyl)-4-methylphenol is the acid of choice for the regio- and stereoselective synthesis of heterocycles **5** via γ-protonation in high yields. Of the remaining protonating agents studied, acetamide proved to be the best acid for the formation of tetrahydrobenzoazaphospholes **4**, although the ratio of α:γ protonated products obtained was rather low. The addition of *tert*-butyldimethylsilyl chloride to the dearomatized lithium species prior to quenching the reaction with methanol allowed us to obtain compounds **4** in high yields and with excellent regio- and stereocontrol. The synthetic applications of tetrahydrobenzoazaphospholes **4** having a [1,3]-cyclohexadiene system are currently under investigation.

Experimental Section

General Procedures. All reactions were carried out under a nitrogen atmosphere using Schlenk techniques. THF was distilled from sodium/benzophenone immediately prior to use. HMPA and DMPU were distilled under reduced pressure from KOH and CaH_2, respectively, and stored over molecular sieves (3Å). Commercial reagents were purchased from Sigma-Aldrich Química S.A. and were distilled prior to use, except for *sec*-BuLi. TLC was performed on Merck plates with aluminum backing and silica gel 60 F_{254}. For column chromatography silica gel 60 (40–63 μm) from Scharlau was used. Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were obtained in KBr pellets using a Mattson Genesis II FTIR spectrophotometer. Mass spectra were determined by APCI on a Hewlett-Packard 1100. NMR spectra were recorded on Bruker Avance 300 and 500 spectrometers using $CDCl_3$ as solvent. Chemical shifts are referred to internal tetramethylsilane for ^{1}H- and ^{13}C, and to external 85% H_3PO_4 for ^{31}P. 2D- NMR correlation spectra (gCOSY, gTOCSY, gNOESY, gHMQC and gHMBC) and selective 1D- gTOCSY and gNOESY were acquired using standard Bruker software and processing routines.

Phosphinamides **1a–c** were prepared following literature procedures.[13] Azaphospholes **4a–9a**, **4b–5b**, **4c–5c**, **8c–10c**, have been characterized previously.[10,13]

General procedure for the preparation of phosphinamides 1d and 1e

To a solution of chlorodiphenylphosphine oxide (3.6 mL, 19.03 mmol) and triethylamine (6.6 mL, 47.57 mmol) in toluene (100 mL) at –78 ºC was added the appropriate amine (cyclohexylamine, 2.2 mL, 19.03 mmol; *p*-methoxyaniline, 2.3g, 19.03 mmol). The mixture was stirred during 1 h, allowing the solution to reach room temperature. The reaction was poured into ice water and extracted with ethyl acetate (3x15 mL) and washed with 1*M* NaOH (2x15 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo* affording **11b** and **11c** as white solids. Then, **11b** (5.5g, 18.37 mmol) and **11c** (6.0g, 18.56 mmol) were treated at room temperature with NaH (1.3g, 36.74 mmol and 1.3g 37.12 mmol, respectively) in THF during 30 min and then benzyl bromide (2.4 mL, 20.21 mmol and 2.5 mL, 20.42 mmol, respectively) was added at the same temperature. Stirring was continued during 1h, and after the aqueous workup described above, compounds **1d** and **1e** were isolated as white solids. The purity of both phosphinamides was higher than 97% (NMR) and they were used without further purification in the next synthetic steps. **1d**; Yield: 90–95%. M.p. 136–137 ºC. ^{1}H- NMR δ 1.10–0.79 (m, 3H), 1.46–1.28 (m, 3H), 1.62 (m, 2H, $^3J_{HH}$ 13.1 Hz), 1.84 (m, 2H, $^3J_{HH}$ 11.3 Hz), 3.22 (dtt, 1H, $^3J_{PH}$ 7.9, $^3J_{HH}$ 11.7, $^4J_{HH}$ 3.3 Hz), 4.25 (d, 1H, $^3J_{HH}$ 11.7 Hz), 7.49–7.13 (m, 11H, ArH), 7.89 (m, 4H). ^{13}C- NMR δ 25.34 (CH_2), 26.27 (CH_2), 32.85 (d, $^3J_{PC}$ 3.6 Hz, CH_2), 46.41 (d, $^2J_{PC}$ 4.2 Hz, CH2), 57.45 (d, $^2J_{PC}$ 3.6 Hz, CH), 126.57 (CAr), 127.53 (CAr), 128.07 (d, $^3J_{PC}$ 13.8 Hz, CAr), 128.33 (CAr), 131.45 (d, $^4J_{PC}$ 2.4 Hz, CAr), 132.29 (d, $^2J_{PC}$ 9.0 Hz, CAr), 132.57 (d, $^1J_{PC}$ 127.4 Hz, C_{ipso}), 140.96 (d, $^3J_{PC}$ 4.2 Hz, C_{ipso}). ^{31}P NMR δ 32.82. MS (APCI-ES), *m/e*: 392 (M+2, 16), 390 (M+1, 100). Analysis: Calcd (%) for $C_{25}H_{28}NOP$: C, 77.10; H, 7.25; N, 3.60. Found: C, 77.06; H, 7.12; N, 3.62. **1e**; Yield: 85–90%. M.p. 146–148 ºC. ^{1}H- NMR δ 3.64 (s, 3H), 4.53 (d, 2H, $^3J_{PH}$ 8.8 Hz), 6.56 (m, 2H, $^3J_{HH}$ 8.8 Hz), 7.06 (d, 2H, $^3J_{HH}$ 8.8 Hz), 7.48–7.14 (m, 11H, ArH), 7.93 (m, 4H). ^{13}C- NMR δ 55.08 (CH_3), 55.14 (d, $^2J_{PC}$ 4.5 Hz, CH_2), 113.73 (CAr), 127.12 (CAr), 128.05 (CAr), 128.25 (d, $^3J_{PC}$ 12.4 Hz, CAr), 128.95 (CAr), 129.97 (d, $^3J_{PC}$ 4.5 Hz, CAr), 131.50 (d, $^2J_{PC}$ 2.5 Hz, CAr), 131.89 (d, $^1J_{PC}$ 129.8 Hz, C_{ipso}), 132.64 (d, $^2J_{PC}$ 9.1 Hz, CAr), 135.15 (C_{ipso}), 137.47 (d, $^3J_{PC}$ 5.0 Hz, C_{ipso}), 157.11 (C_{ipso}). ^{31}P- NMR δ 28.31. MS (APCI-ES):

m/e, 414 (M+2, 78), 413 (M+1, 100). Analysis: Calcd (%) for $C_{26}H_{24}NO_2P$: C, 75.53; H, 5.85; N, 3.39. Found: C, 75.16; H, 5.72; N, 3.32.

General procedure for the preparation of phosphinamide 1f

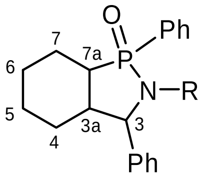
To a solution of 2-benzylaminopyridine (2.0g , 10.64 mmol) in THF (40–60 mL) at –30 ºC was added dropwise a solution of *n*-BuLi (6.7 mL of a 1.6 *M* solution in cyclohexane, 10.64 mmol). After 1 h of metallation, the bath was cooled down at –78 ºC, and chlorodiphenylphosphine oxide (2.1 mL, 10.64 mmol) added. The mixture was stirred for 0.5 to 1 h until a colorless solution was obtained. The reaction was poured into ice water and extracted with ethyl acetate (3x15 mL) and washed with 1*M* NaOH (2x15 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo* affording **1f** as a white solid in quantitative yield. **1f.** Yield: 90–95%. M.p. 125–126 ºC. ^{1}H- NMR δ 5.04 (d, 2H, $^3J_{PH}$ 11.2 Hz), 6.73 (dd, 1H, $^3J_{HH}$ 7.0, $^3J_{HH}$ 4.9 Hz), 7.04 (d, 1H, $^3J_{HH}$ 8.4 Hz), 7.51–7.12 (m, 11H, ArH), 7.86 (m, 4H). 8.11 (dd, 1H, $^3J_{HH}$ 4.9, $^4J_{HH}$ 1.8 Hz). ^{13}C- NMR δ 50.13 (d, $^2J_{PC}$ 3.6 Hz, CH_2), 115.22 (d, $^3J_{PC}$ 3.0 Hz, CAr), 117.73 (CAr), 126.78 (CAr), 127.27 (CAr), 128.22 (d, $^3J_{PC}$ 13.2 Hz, CAr), 128.24 (CAr), 131.63 (d, $^4J_{PC}$ 3.0 Hz, CAr), 132.04 (d, $^1J_{PC}$ 129.8 Hz, C_{ipso}), 132.39 (d, $^2J_{PC}$ 10.2 Hz, CAr), 137.21 (CAr), 138.42 (C_{ipso}), 147.31 (CAr), 155.80 (C_{ipso}). ^{31}P- NMR δ 29.48. MS (APCI-ES), *m/e*: 387 (M+3, 8), 386 (M+2, 22), 385 (M+1, 100). Analysis: Calcd (%) for $C_{24}H_{21}N_2OP$: C, 74.99; H, 5.51; N, 7.29. Found: C, 74.76; H, 5.52; N, 7.02.

General procedure for the synthesis of tetrahydro benzo[*c*][1,2]-1λ^5-azaphospholes, 4–18

To a solution of the appropriate phosphinamide **1a–e** (6.23x 10^{-4} mol) and HMPA (3.72x10^{-3} mol) in THF (30 mL) was added a solution of *sec*-BuLi (1.2 mL of a 1.3 *M* solution in cyclohexane, 1.56x 10^{-3} mol) at –90 ºC. After 30 min of metallation was added the corresponding proton source (3.12x 10^{-3} mol). The reaction mixture was stirred at –90 ºC for 30 min, except for *p*-toluenesulfonic acid where the time was increased to 12 h owing to insolubility problems. Then the reaction mixture was poured into ice water and extracted with ethyl acetate (3x15 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 a mixture of ethyl acetate:hexane, 1:1 as eluent. The same procedure was applied when the reaction was carried out in the presence of DMPU (3.72x 10^{-3} mol) as co-solvent.

General procedure for the improved synthesis of tetrahydro benzo[*c*][1,2]-1λ^5-azaphospholes, 4

To a solution of the appropriate phosphinamide **1a–d** (6.23x 10^{-4} mol) and HMPA (3.72x 10^{-3} mol) in THF (30 mL) was added a solution of *sec*-BuLi (1.2 mL of a 1.3 M solution in cyclohexane, 1.56x 10^{-3} mol) at –90 ºC. After 30 (**1a**,**b**) or 60 (**1c**,**d**) min of metallation was added *tert*-butyldimethylsilyl chloride (0.24 g, 1.56 x 10^{-3} mol) and stirring was continued during 30 min. Then methanol (1 mL) was added at –90 ºC, and allowed to react at this temperature for other 30 min. The reaction mixture was poured after into ice water and extracted with ethyl acetate (3x15 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. ^{1}H-, ^{1}H{^{31}P}- and ^{31}P{^{1}H}- NMR spectra of the crude reaction mixture were measured in order to determine the stereoselectivity of the process. The crude reaction mixture was then purified by flash chromatography using a mixture of ethyl acetate:hexane 1:1 as eluent. The same procedure was applied when the reaction was carried out in the presence of DMPU (3.72x 10^{-3} mol) as co-solvent.



(1S_PR_P, 3*RS*, 3a*RS*, 7a*RS*)-2-*tert*-butyl-1,3-diphenyl-2,3,3a,7a-tetrahydrobenzo[c][1,2]-azaphosphole 1-oxide (18c). Yield after chromatography (ethyl acetate:hexane, 1:1) 18% (0.034g, protonation with TBDMSCl-**A1**). M.p. 215–216 °C; ^{1}H- NMR δ 1.10 (s, 9H), 3.02 (tt, 1H, J_{PH} 12.7, J 12.7, J 2.7 Hz), 3.44 (m, 1H, J 12.7, J 7.5 Hz), 4.73 (dd, 1H, J_{PH} 19.9, J 7.5 Hz), 5.47 (m, 1H, J_{PH} 1.84, J 9.6, J 6.3, J 3.5 Hz), 5.57 (m, 2H), 5.95 (m, 1H, J_{PH} 9.6, J 9.6, J 2.7 Hz), 7.04 (m, 1H, J 6.4, J 2.2 Hz), 7.12–7.25 (m, 2H), 7.46–7.54 (m, 3H), 7.93 (m, 2H, J_{PH} 12.2 Hz), 8.10 (m, 1H, J 6.4, J 2.2 Hz); ^{13}C- NMR δ 30.60 (d, CH_3, J_{PC} 2.4 Hz), 38.24 (d, CH, J_{PC} 91.3 Hz), 39.98 (d, CH, J_{PC} 1.2 Hz), 55.30 (d, C, J_{PC} 3.0 Hz), 67.17 (d, CH, J_{PC} 22.8 Hz), 121.10 (d, HC=, J_{PC} 7.2 Hz), 122.83 (d, HC=, J_{PC} 10.8 Hz), 123.93 (d, HC=, J_{PC} 10.2 Hz), 125.25 (d, HC=, J_{PC} 3.0 Hz), 125.84–128.16 (4x CAr), 128.42 (d, CAr, J_{PC} 13.2 Hz), 129.09 (CAr), 131.21 (d, CAr, J_{PC} 3.0 Hz), 131.42 (d, CAr, J_{PC} 10.2 Hz), 137.39 (d, C_{ipso}, J_{PC} 121.9 Hz), 142.24 (C_{ipso}); ^{31}P- NMR δ 47.28; MS (APCI-ES) *m/e* 364 (M+1). Anal. Calcd (%) for $C_{23}H_{26}NOP$: C, 76.01; H, 7.21; N, 3.85. Found: C, 76.21; H, 7.23; N, 3.82.

(1S_PR_P, 3*SR,* 3a*RS*, 7a*RS*)-2,3,3a,7a-Tetrahydro- 2-cyclohexyl-1,3-diphenylbenzo[*c*]-[1,2]-azaphosphole 1-oxide (4d). Yield after chromatography (ethyl acetate:hexane, 1:1) 42% (0.084g, protonation with **A15**). An oil. ^{1}H- NMR δ 1.95–0.79 (m, 10H), 2.71 (dtt, 1H, $^3J_{PH}$ 18.5, $^3J_{HH}$ 11.7, $^3J_{HH}$ 3.4 Hz), 2.92 (ddd, 1H, $^3J_{HH}$ 10.6, $^3J_{HH}$ 9.1, $^3J_{HH}$ 5.7 Hz), 2.99 (m, 1H, $^2J_{PH}$ 24.9, $^3J_{HH}$ 10.6 Hz), 4.57 (d, 1H, $^3J_{HH}$ 9.1 Hz), 5.39 (ddd, 1H, $^3J_{HH}$ 9.5, $^3J_{HH}$ 5.7 Hz), 6.02 (dd, 1H, $^3J_{HH}$ 9.8, $^3J_{HH}$ 5.3 Hz), 6.07 (m, 1H, $^3J_{HH}$ 9.8, $^3J_{HH}$ 4.9, $^4J_{HH}$ 3.0 Hz), 6.17 (m, 1H), 7.57–7.30 (m, 8H), 8.07 (m, 2H). ^{13}C- NMR δ 25.32 (CH_2), 25.46 (CH_2), 26.26 (CH_2), 31.15 (CH_2), 31.78 (CH_2), 38 .76 (d, $^1J_{PC}$ 85.3 Hz, CH), 42.69 (CH), 55.29 (CH), 66.87 (d, $^3J_{PC}$ 21.0 Hz, CH), 119.78 (d, $^2J_{PC}$ 8.4 Hz, HC=), 123.61 (d, $^3J_{PC}$ 12.0 Hz, HC=), 124.51 (d, $^3J_{PC}$ 12.3 Hz, HC=), 124.56 (d, $^4J_{PC}$ 0.9 Hz, HC=), 131.54 (d, $^2J_{PC}$ 10.2 Hz, CAr), 131.40 (d, $^4J_{PC}$ 3.0 Hz, CAr), 128.65–127.49 (7x CAr), 136.68 (d, $^1J_{PC}$ 126.8 Hz, C_{ipso}), 140.69 (d, $^3J_{PC}$ 10.2 Hz, C_{ipso}). ^{31}P-NMR δ 48.83. MS (APCI-ES), *m/e*: 390 (M+1, 100), 380 (40), 300 (35). Analysis: Calcd (%) for $C_{25}H_{28}NOP$: C, 77.10; H, 7.25; N, 3.60. Found: C, 77.23; H, 7.27; N, 3.58.

(1*S*$_{P}$*R*$_{P}$, 3*SR*, 3a*RS*)-2,3,3a,6-Tetrahydro-2-cyclohexyl-1,3-diphenylbenzo[*c*][1,2]-azaphosphole 1-oxide (5d). Yield after chromatography (ethyl acetate:hexane, 1:1) 98% (0.196g, protonation with **A6**). Oil. ^{1}H- NMR δ 2.01–0.68 (m, 10H), 2.63 (m, 1H), 2.74 (ddddd, 1H, $^{4}J_{\mathrm{PH}}$ 4.8, $^{2}J_{\mathrm{HH}}$ 23.5, $^{3}J_{\mathrm{HH}}$ 12.1, $^{3}J_{\mathrm{HH}}$ 4.7, $^{4}J_{\mathrm{HH}}$ 2.6 Hz), 2.86 (m, 1H, $^{2}J_{\mathrm{HH}}$ 23.5, $^{3}J_{\mathrm{HH}}$ 7.0, $^{3}J_{\mathrm{HH}}$ 4.4 Hz), 3.21 (m, 1H), 4.36 (d, 1H, $^{3}J_{\mathrm{HH}}$ 9.5 Hz), 5.51 (m, 1H, $^{3}J_{\mathrm{HH}}$ 9.9 Hz), 5.74 (m, 1H, $^{3}J_{\mathrm{HH}}$ 9.9 Hz), 6.60 (d, 1H, $^{3}J_{\mathrm{PH}}$ 16.4 Hz), 7.53–7.29 (m, 8H, ArH), 8.08 (m, 2H). ^{13}C- NMR δ 25.26 (CH$_2$), 25.48 (CH$_2$), 26.24 (CH$_2$), 27.55 (d, $^{3}J_{\mathrm{PC}}$ 12.6 Hz, CH$_2$), 31.18 (CH$_2$), 31.68 (CH$_2$), 45 .85 (d, $^{2}J_{\mathrm{PC}}$ 13.8 Hz, CH), 55.56 (CH), 66.69 (d, $^{3}J_{\mathrm{PC}}$ 12.0 Hz, CH), 122.75 (d, $^{3}J_{\mathrm{PC}}$ 6.6 Hz, HC=), 125.22 (HC=), 128.84–127.67 (7x CAr), 131.29 (d, $^{4}J_{\mathrm{PC}}$ 3.0 Hz, CAr), 131.65 (d, $^{2}J_{\mathrm{PC}}$ 10.2 Hz, CAr), 133.89 (d, $^{2}J_{\mathrm{PC}}$ 9.6 Hz, HC=), 133.97 (d, $^{1}J_{\mathrm{PC}}$ 120.8 Hz, C=), 136.50 (d, $^{1}J_{\mathrm{PC}}$ 133.4 Hz, C$_{ipso}$), 139.97 (d, $^{3}J_{\mathrm{PC}}$ 9.0 Hz, C$_{ipso}$). ^{31}P- NMR δ 27.80. MS (APCI-ES), *m/e*: 414 (M+1+Na, 100), 390 (M+1, 24), 323 (45), 201 (25). Analysis: Calcd (%) for $C_{25}H_{28}NOP$: C, 77.10; H, 7.25; N, 3.60. Found: C, 77.01; H, 7.19; N, 3.53.

(1*S*$_{P}$*R*$_{P}$, 3*SR*, 3a*RS*, 7a*SR*)-2,3,3a,7a-Tetrahydro-2-cyclohexyl-1,3-diphenylbenzo-[*c*][1,2]-aza phosphole 1-oxide (8d). Yield after chromatography (ethyl acetate:hexane, 1:1) 36% (0.072g, protonation with **A6**). Oil. ^{1}H- NMR δ 1.95–0.74 (m, 10H), 2.71 (m, 1H), 2.81 (m, 1H, $^{3}J_{\mathrm{HH}}$ 20.6), 2.89 (m, 1H, $^{3}J_{\mathrm{PH}}$ 22.8, $^{3}J_{\mathrm{HH}}$ 20.6, $^{3}J_{\mathrm{HH}}$ 1.5 Hz), 4.56 (d, 1H, $^{3}J_{\mathrm{HH}}$ 10.3 Hz), 5.97–5.67 (m, 4H), 7.76–7.02 (m, 8H, ArH), 8.07 (m, 2H). ^{13}C- NMR δ 25.49 (CH$_2$), 25.72 (CH$_2$), 26.22 (CH$_2$), 31.41 (CH$_2$), 31.48 (CH$_2$), 42 .90 (d, $^{1}J_{\mathrm{PC}}$ 93.0 Hz, CH), 45.66 (d, $^{2}J_{\mathrm{PC}}$ 2.5 Hz, CH), 55.33 (d, $^{2}J_{\mathrm{PC}}$ 0.8 Hz, CH), 64.42 (d, $^{3}J_{\mathrm{PC}}$ 8.7 Hz, CH), 122.84 (HC=), 126.21 (d, $^{3}J_{\mathrm{PC}}$ 11.0 Hz, HC=), 126.32 (HC=), 127.39 (d, $^{2}J_{\mathrm{PC}}$ 8.8 Hz, HC=), 128.95–127.78 (7x CAr), 131.63 (d, $^{4}J_{\mathrm{PC}}$ 3.4 Hz, CAr), 132.49 (d, $^{2}J_{\mathrm{PC}}$ 9.9 Hz, CAr), 134.66 (d, $^{1}J_{\mathrm{PC}}$ 125.3 Hz, C$_{ipso}$), 138.98 (d, $^{3}J_{\mathrm{PC}}$ 7.9 Hz, C$_{ipso}$). ^{31}P- NMR δ 40.85. MS (APCI-ES), *m/e*: 391 (M+2, 25), 390 (M+1, 100), 380 (17), 323 (42). Analysis: Calcd (%) for $C_{25}H_{28}NOP$: C, 77.10; H, 7.25; N, 3.60. Found: C, 77.13; H, 7.20; N, 3.51.

(1*S*$_{P}$*R*$_{P}$, 3*SR*, 3a*RS*, 7a*RS*)-2,3,3a,7a-Tetrahydro- 2-(*para*-methoxyphenyl)-1,3-diphenylbenzo[*c*][1,2]azaphosphole 1-oxide (4e). Yield after chromatography (ethyl acetate:hexane, 1:1) 30% (0.06g, protonation with **A1**). Oil. ^{1}H- NMR δ 3.13 (dddd, 1H, $^{2}J_{\mathrm{PH}}$ 3.7, $^{3}J_{\mathrm{HH}}$ 10.1, $^{3}J_{\mathrm{HH}}$ 9.2, $^{4}J_{\mathrm{HH}}$ 5.5 Hz), 3.25 (m, 1H, $^{3}J_{\mathrm{PH}}$ 11.0, $^{3}J_{\mathrm{HH}}$ 10.1, $^{4}J_{\mathrm{HH}}$ 2.9 Hz), 3.62 (s, 3H), 4.99 (d, 1H, J_{HH} 9.2 Hz), 5.58 (m, $^{3}J_{\mathrm{HH}}$ 5.4 Hz), 6.13 (m, 1H), 6.16 (m, 1H, $^{3}J_{\mathrm{PH}}$ 5.4, $^{3}J_{\mathrm{HH}}$ 9.3 Hz), 6.27 (m, 1H), 6.58 (m, 2H, $^{3}J_{\mathrm{HH}}$ 9.1 Hz), 6.77 (m, 2H, $^{3}J_{\mathrm{HH}}$ 9.1 Hz), 7.66–7.25 (m, 8H, ArH), 8.10 (m, 2H). ^{13}C- NMR δ 38.61 (d, $^{1}J_{\mathrm{PC}}$ 84.8 Hz, CH), 42.77 (CH), 55.18 (CH$_3$), 68.65 (d, $^{2}J_{\mathrm{PC}}$ 21.9 Hz, CH), 114.16 (CAr), 119.40 (d, $^{3}J_{\mathrm{PC}}$ 8.3 Hz, HC=), 123.52 (d, $^{3}J_{\mathrm{PC}}$ 11.6 Hz, HC=), 124.42 (d, $^{3}J_{\mathrm{PC}}$ 2.9 Hz, CAr), 125.06 (d, $^{4}J_{\mathrm{PC}}$ 2.1 Hz, HC=), 125.15 (d, $^{2}J_{\mathrm{PC}}$ 5.0 Hz, HC=), 128.96–127.22 (7x CAr), 131.70 (d, $^{2}J_{\mathrm{PC}}$ 9.9 Hz, CAr), 132.11 (d, $^{4}J_{\mathrm{PC}}$ 2.9 Hz, CAr), 134.00 (C$_{ipso}$), 134.35 (d, $^{1}J_{\mathrm{PC}}$ 125.7 Hz, C$_{ipso}$), 139.97 (d, $^{3}J_{\mathrm{PC}}$ 8.7 Hz, C$_{ipso}$), 155.85 (C$_{ipso}$). ^{31}P- NMR δ 47.55. MS (APCI-ES), *m/e*, 437 (M+1+Na, 30), 436 (M+Na). Analysis: Calcd (%) for $C_{26}H_{25}NO_2P$: C, 75.53; H, 5.85; N, 3.39. Found: C, 75.43; H, 5.80; N, 3.41.

(1*R*$_{P}$*S*$_{P}$, 3*SR*, 3a*RS*)-2,3,3a,6-Tetrahydro-2-(*para*-methoxyphenyl)-1,3-diphenylbenzo[*c*]-[1,2]azaphosphole 1-oxide (5e). Yield after chromatography (ethyl acetate:hexane, 1:1) 40%

(0.08g, protonation with **A6**). Oil, decomposes. ^{1}H- NMR δ 2.82 (m, 1H, J_{HH} 23.3, J_{HH} 11.7, J_{HH} 4.8, J_{HH} 2.2 Hz), 2.96 (m, 1H, J_{HH} 23.3 Hz), 3.44 (m, 1H), 3.60 (s, 3H), 4.74 (d, 1H, $^{3}J_{HH}$ 9.5 Hz), 5.67 (m, 1H, $^{3}J_{HH}$ 10.3, $^{3}J_{HH}$ 2.2 Hz), 5.86 (m, 1H, $^{3}J_{HH}$ 10.3 Hz), 6.56 (m, 2H, $^{3}J_{HH}$ 8.8 Hz), 6.77 (m, 2H, $^{3}J_{HH}$ 8.8 Hz), 6.81 (m, 1H), 7.64–7.19 (m, 8H, ArH), 8.08 (m, 2H). ^{13}C- NMR δ 27.67 (d, $^{3}J_{PC}$ 12.9 Hz, CH_2), 46.17 (d, $^{2}J_{PC}$ 13.4 Hz, CH), 55.11 (CH_3), 69.18 (d, $^{2}J_{PC}$ 13.4 Hz, CH), 114.15 (CAr), 122.53 (d, $^{3}J_{PC}$ 6.5 Hz, HC=), 125.49 (d, $^{4}J_{PC}$ 1.4 Hz, HC=), 125.96 (d, $^{3}J_{PC}$ 2.8 Hz, CAr), 128.94–127.63 (7x CAr), 131.69 (d, $^{2}J_{PC}$ 10.6 Hz, CAr), 132.93 (d, $^{1}J_{PC}$ 104.0 Hz, C=), 132.27 (d, $^{4}J_{PC}$ 2.8 Hz, CAr), 132.40 (C_{ipso}), 134.30 (d, $^{1}J_{PC}$ 133.6 Hz, C_{ipso}), 135.77 (d, $^{2}J_{PC}$ 9.2 Hz, HC=), 139.13 (d, $^{3}J_{PC}$ 7.9 Hz, C_{ipso}), 156.36 (d, $^{5}J_{PC}$ 1.4 Hz, C_{ipso}). ^{31}P- NMR δ 27.19. MS (APCI-ES), *m/e*: 415 (M+2, 25), 414 (M+1, 100). Analysis: Calcd (%) for $C_{26}H_{25}NO_2P$: C, 75.53; H, 5.85; N, 3.39. Found: C, 75.47; H, 5.77; N, 3.33.

(1*R*

(1R_PS_P, 3*RS*, 3a*RS*)-2,3,3a,6-Tetrahydro-2-(*para*-methoxyphenyl)-1,3-diphenylbenzo[*c*]-[1,2]azaphosphole 1-oxide (10e). Yield after chromatography (ethyl acetate:hexane, 1:1) 9% (0.018g, protonation with **A6**). Oil. ^{1}H- NMR δ 2.69 (m, 2H), 3.64 (s, 3H), 3.97 (m, 1H), 5.36 (dd, 1H, $^{3}J_{PH}$ 14.6, $^{3}J_{HH}$ 8.1 Hz), 5.51 (m, 2H), 6.65 (m, 2H, $^{3}J_{HH}$ 9.2 Hz), 6.83 (m, 1H, $^{3}J_{PH}$ 17.3, $^{3}J_{HH}$ 2.9 Hz), 7.62–7.03 (m, 10H, ArH), 7.12 (m, 2H, $^{3}J_{HH}$ 9.2 Hz), 7.91 (m, 2H). ^{13}C- NMR δ 27.02 (d, $^{3}J_{PC}$ 12.9 Hz, CH_2), 40.29 (d, $^{2}J_{PC}$ 16.4 Hz, CH), 55.23 (CH_3), 66.83 (d, $^{2}J_{PC}$ 10.9 Hz, CH), 114.37 (CAr), 121.09 (d, $^{3}J_{PC}$ 4.3 Hz, CAr), 122.95 (d, $^{3}J_{PC}$ 7.0 Hz, HC=), 124.50 (d, $^{4}J_{PC}$ 1.6 Hz, HC=), 128.95–127.59 (7x CAr), 131.31 (d, $^{1}J_{PC}$ 127.5 Hz, C_{ipso}), 131.51 (d, $^{4}J_{PC}$ 2.7 Hz, CAr), 131.80 (d, $^{2}J_{PC}$ 10.6 Hz, CAr), 132.70 (d, $^{1}J_{PC}$ 120.1 Hz, C=), 134.03 (d, $^{3}J_{PC}$ 3.9 Hz, C_{ipso}), 136.73 (d, $^{2}J_{PC}$ 10.2 Hz, HC=), 138.52 (C_{ipso}), 154.85 (C_{ipso}). ^{31}P- NMR δ 26.05. MS (APCI-ES), *m/e*: 415 (M+2, 21), 414 (M+1, 100), 291 (7). Analysis: Calcd (%) for $C_{26}H_{25}NO_2P$: C, 75.53; H, 5.85; N, 3.39. Found: C, 75.37; H, 5.70; N, 3.30.

(1S_PR_P, 3*SR*, 3a*RS*)-2,3,3a,6-Tetrahydro-2-(*para*-methoxyphenyl)-1,3-diphenylbenzo[*c*]-[1,2]azaphosphole 1-oxide (16e). Yield after chromatography (ethyl acetate:hexane, 1:1) 9% (0.017g, protonation with **A6**). Oil. ^{1}H- NMR δ 2.81 (m, 2H), 3.55 (s, 3H), 3.56 (m, 1H), 4.70 (d, 1H, $^{3}J_{HH}$ 9.2 Hz), 5.78 (m, 1H, $^{3}J_{HH}$ 9.9 Hz), 5.88 (m, 1H, $^{3}J_{HH}$ 9.9 Hz), 6.23 (m, 1H, $^{3}J_{PH}$ 17.6, $^{3}J_{HH}$ 3.3 Hz), 6.48 (m, $^{3}J_{HH}$ 8.8 Hz), 6.98 (m, $^{3}J_{HH}$ 8.8 Hz), 7.61–7.17 (m, 8H, ArH), 7.87 (m, 2H). ^{13}C- NMR δ 27.23 (d, $^{3}J_{PC}$ 13.6 Hz, CH_2), 44.34 (d, $^{2}J_{PC}$ 15.3 Hz, CH), 54.97 (CH_3), 70.57 (d, $^{2}J_{PC}$ 12.0 Hz, CH), 113.78 (CAr), 122.50 (d, $^{3}J_{PC}$ 3.3 Hz, CAr), 122.99 (d, $^{3}J_{PC}$ 7.4 Hz, HC=), 125.29 (d, $^{4}J_{PC}$ 1.2 Hz, HC=), 131.24 (d, $^{1}J_{PC}$ 112.9 Hz, C=), 133.62–127.44 (10x CAr), 133.04 (d, $^{2}J_{PC}$ 12.4 Hz, HC=), 133.59 (d, $^{2}J_{PC}$ 4.5 Hz, C_{ipso}), 133.79 (d, $^{1}J_{PC}$ 127.8 Hz, C_{ipso}), 139.43 (d, $^{3}J_{PC}$ 3.7 Hz, C_{ipso}), 155.06 (C_{ipso}). ^{31}P- NMR δ 27.42. MS (APCI-ES), *m/e*: 436 (M+Na, 10), 415 (M+2, 33), 414 (M+1, 100). Analysis: Calcd (%) for $C_{26}H_{25}NO_2P$: C, 75.53; H, 5.85; N, 3.39. Found: C, 75.44; H, 5.60; N, 3.22.

(*para*-Methoxyphenylamino)benzyldiphenylphosphine oxide (17e). Yield after chromatography (ethyl acetate:hexane 1:1) 9% (0.016g, protonation with **A6**). Oil. ^{1}H- NMR δ 3.69 (s, 1H), 4.92 (br, NH), 5.14 (d, 1H, $^{2}J_{PH}$ 11.4 Hz), 6.56 (m, 2H, $^{3}J_{HH}$ 8.8 Hz), 6.68 (m, 2H, $^{3}J_{HH}$ 8.8 Hz), 7.63–7.10 (m, 13H, ArH), 7.88 (m, 2H). ^{13}C- NMR δ 55.57 (CH_3), 58.24 (d, $^{1}J_{PC}$ 75.3 Hz, CH), 114.70 (CAr), 115.16 (CAr), 128.75–127.52 (9x CAr), 130.23 (d, $^{1}J_{PC}$ 100.1 Hz, C$_{ipso}$), 130.84 (d, $^{1}J_{PC}$ 97.2 Hz, C$_{ipso}$), 131.60 (d, $^{2}J_{PC}$ 9.1 Hz, CAr), 131.67 (d, $^{2}J_{PC}$ 8.7 Hz, CAr), 131.82 (d, $^{4}J_{PC}$ 2.9 Hz, CAr), 132.17 (d, $^{4}J_{PC}$ 2.9 Hz, CAr), 135.14 (d, $^{2}J_{PC}$ 1.7 Hz, CAr), 140.06 (d, $^{3}J_{PC}$ 12.8 Hz, C$_{ipso}$), 152.54 (C$_{ipso}$). ^{31}P- NMR δ 34.14. MS (APCI-ES), *m/e*: 437 (M+1+Na, 66), 436 (M+Na, 100), 212 (65). Analysis: Calcd (%) for $C_{26}H_{24}NO_2P$: C, 75.53; H, 5.85; N, 3.39. Found: C, 75.33; H, 5.70; N, 3.31.

(2-Pyridylamino)benzyldiphenylphosphine oxide (17f). Precipitated in Et$_2$O, (0.195g) 96 %. ^{1}H- NMR δ 6.31 (dd, 1H, $^{2}J_{PH}$ 8.9, $^{3}J_{HH}$ 9.8 Hz), 6.59–6.48 (m, 2H), 6.52 (d, NH, $^{3}J_{HH}$ 9.8 Hz), 7.58–7.01 (m, 13H, ArH), 7.96 (dd, 2H, $^{3}J_{PH}$ 7.3, $^{3}J_{HH}$ 11.3 Hz), 8.06 (d, 1H, $^{3}J_{HH}$ 4.0 Hz). ^{13}C-NMR δ 53.50 (d, $^{1}J_{PC}$ 76.9 Hz, CH), 109.62 (CAr), 113.45 (CAr), 128.82–127.33 (9x CAr), 131.05 (d, $^{1}J_{PC}$ 97.9 Hz, C$_{ipso}$), 131.09 (d, $^{1}J_{PC}$ 98.5 Hz, C$_{ipso}$), 131.32 (d, $^{2}J_{PC}$ 9.0 Hz, CAr), 131.44 (d, $^{2}J_{PC}$ 9.0 Hz, CAr), 131.63 (d, $^{4}J_{PC}$ 3.0 Hz, CAr), 131.90 (d, $^{4}J_{PC}$ 2.4 Hz, CAr), 135.81 (C$_{ipso}$), 136.95 (CAr), 147.53 (CAr), 156.86 (d, $^{3}J_{PC}$ 8.4 Hz, C$_{ipso}$). ^{31}P- NMR δ 33.82. MS (APCI-ES), *m/e*: 386 (M+2, 12), 385 (M+1, 46), 184 (15), 183 (100). Analysis: Calcd (%) for $C_{24}H_{21}N_2OP$: C, 74.99; H, 5.51; N, 7.29. Found: C, 74.93; H, 5.50; N, 7.21.

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Supplementary Information

^{1}H- and ^{31}P{^{1}H}- NMR spectra of the crude mixture leading to **4a**–**d** via dearomatization-silylation-methanolysis. ^{1}H-, ^{31}P{^{1}H}-, and 2D- gNOESY NMR spectra of **4d**, **5d**, and **18c**.

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