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Dearomatizing Anionic Cyclizations of *N*-Benzyl-*N*-methyldiphenylphosphinamides. Synthesis of γ-(*N*-Methylamino)phosphinic Acids

Ignacio Fernández,[†] Fernando López Ortiz,*[,†] Baudilio Tejerina,[†] and Santiago García Granda[‡]

Área de Química Orgánica, Universidad de Almería, Carretera de Sacramento s/n, 04120 Almería, Spain, and Departamento de Química Física y Analítica, Universidad de Oviedo, Avda. Julián Clavería 8, 33071 Oviedo, Spain

flortiz@ual.es

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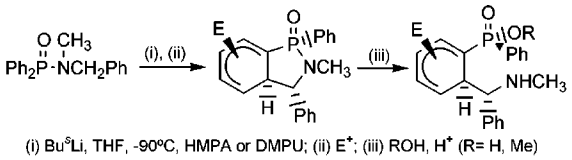
ABSTRACT



The first dearomatizing anionic reaction of a phenyl ring promoted by an *N*-benzyl-*N*-methylphosphinamide group is described. The intermediate lithium species can be trapped with different electrophiles, affording tetrahydrobenzo[*c*]-1-aza-2λ⁵-phospholes with excellent diastereoselectivity. The new process is a simple and very efficient entry to the stereoselective synthesis of functionalized γ-(*N*-methylamino)phosphinic acids and esters.

Dearomatizing reactions through sequential addition of a nucleophile and an electrophile to activated benzenes is a very useful methodology for the synthesis of regio- and stereoselectively substituted cyclohexadiene derivatives. The activation may be achieved by transition metal coordination to the π system[1] or through classical electron-withdrawing groups: aldehydes, ketones, esters of carboxylic acids,[2] and imines.[3,4] For phenyl sulfones[5] and sulfonamides,[6] the nucleophilic dearomatization can be carried out intramolecularly. Very recently, Clayden et al. have extended this anionic cyclization to the dearomatization of lithium tertiary *N*-benzylbenzamides.[7] The intermediate dearomatized enolate

[†] Universidad de Almería.
[‡] Universidad de Oviedo.

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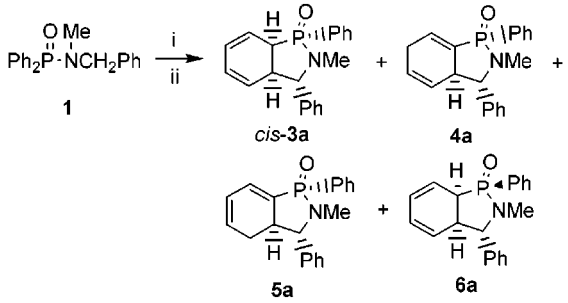
has been quenched with several electrophiles with high stereocontrol.

Tertiary phosphonamides are good activating groups for the *ortho*-lithiation of aromatic rings.[8] Furthermore, the reaction of *N*-benzyl-*N*-methyldiphenylthiophosphinamide with Bu^{s}Li in THF/TMEDA also affords the *ortho*-lithiated derivative.[9] We report here the first anionic highly stereoselective cyclization of tertiary *N*-benzyl-*N*-methyldiphenylphosphinamides which results in the dearomatization of one of the phenyl rings bonded to the phosphorus. The tetrahydrobenzo[*c*]-1-aza-2λ^5phospholes obtained are readily transformed in functionalized *N*-methylaminophosphinic acids and esters.

N-Benzyl-*N*-methyldiphenylphosphinamide[10] **1** was treated with Bu^{s}Li (1.5 equiv) at −90 °C in THF during 30 min in the presence of HMPA (6 equiv). Quenching the dark red solution obtained with MeOH (20 equiv) at −90 °C gave 1-aza-2λ^5-phospholes *cis*-**3a**:**4a**:**5a**:**6a** in a 72:20:3:5 ratio[11] in 90% total yield[12] (Scheme 1).

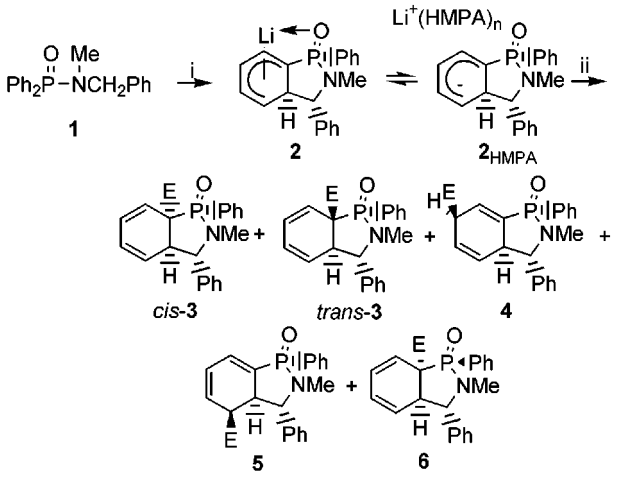
Scheme 1[a]



[a] i. Bu^{s}Li (1.5 equiv), THF −90 °C, HMPA (6 equiv), 30 min; ii. MeOH, 30 min.

Flash chromatography (eluent: ethyl acetate) allowed for the isolation of the major components of the mixture.[13] Thus, high yields of diene *cis*-**3a** (65%, isolated) with four stereogenic centers were obtained. This is the first time that an anionic cyclization with loss of aromaticity is observed in phosphinamides.[14,15] Without HMPA, the yield decreased to 43% and the stereoselectivity of the reaction was also less (Scheme S1, Supporting Information).

Scheme 2[a]



[a] i. Bu^{s}Li (1.5 equiv), THF −90 °C, HMPA (6 equiv), 30 min; ii. E^+ (**a**, E = H; **b**, E = D; **c**, E = Me; **d**, E = PhCHOH), 30−120 min.

The addition of D_2O, a harder electrophile, afforded the mixture of compounds *cis*-**3b**:*trans*-**3b**:**4b**:**5b**:**6b** in a ratio of 22:27:40:8:3 in 88% total yield (Scheme 2, E = D). Significantly, no deuterated phosphinamide was detected, implying that once benzylic deprotonation occurred the resulting anion attacks intramolecularly to a *P*-phenyl ring yielding a new dearomatized phosphorus-stabilized anion of the type **2** and/or **2$_{HMPA}$** (Scheme 2).

Intermediates **2**−**2$_{HMPA}$** have been characterized by NMR monitoring of the metalation step. At −80 °C the ^{31}P spectrum showed a quartet at δ 35.03 [$^2J(^{31}P,^7Li)$ 6.4 Hz] for monomer **2** and a broad singlet at δ 39.8 assigned to **2$_{HMPA}$**. On the basis of the deaggregation power of HMPA, one can assume that **2$_{HMPA}$** is also a monomer.[16] The structural analysis of **2**−**2$_{HMPA}$** indicated that both species have the same bicyclic structure and relative stereochemistry.[13] Hence, **2** can be represented as a contact ion pair with an intramolecular PO···Li coordination, in equilibrium with a solvent-separated ion pair **2$_{HMPA}$** where the lithium cation is fully coordinated to HMPA molecules.[17]

The reaction with IMe was more complex. Besides the dearomatized products *cis*-**3c**:*trans*-**3c**:**4c** (53% yield, ratio

Table 1. Product Distribution in the Cyclization−Addition Reactions

	E^+	*cis*-**3**	*trans*-**3**	**4**	**5**	**6**	yield, %[a]
a	MeOH	65		18	3	4	90[b]
b	D_2O	19	24	35	7	3	88[b]
c	MeI	6	8	39			85[c]
d	PhCHO			80:20[d]			>98

[a] Crude yield. [b] Recovered **1** (5%), byproduct $Ph_2P(O)CH(Me)Et$. [c] Compounds **7** (10%), **7b** (15%), and **8** (7%) were also isolated (see ref 18). [d] ^{31}P NMR ratio of epimers in the C-OH carbon.

(8) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Dashan, L.; Trippett, S. *Tetrahedron Lett.* **1983**, *24*, 2039.

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(10) Phosphinamide **1** was easily prepared in multigram scale by addition of *N*-methylbenzylamine to a toluene solution of chlorodiphenylphosphine and triethylamine (4 equiv) and then in situ oxidation with H_2O_2. Yield 90% (Supporting Information).

(11) Measured from the inverse-gated proton-decoupled ^{31}P NMR spectrum of the crude reaction using a pulse width of 15°, a relaxation delay of 10 s, and an accumulation of 128 scans.

(12) Other products: **1** (4%) and $Ph_2P(O)Bu^s$ (6%).

(13) Structural determinations were based on the analysis of 1D (^{1}H, ^{13}C, ^{31}P, DEPT, selective TOCSY) and 2D (gHMQC, gHMBC, gNOESY, ROESY) NMR experiments. Full details will be published elsewhere.

(14) For benzylic metalation of phosphorus triamides, see: Müller, J. F. K.; Spingler, B.; Zehnder, M. *Synlett* **1997**, 1059.

(15) For an analogous dearomatization of phenylsulphonamides see refs 6a,b.

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6:8:39, Table 1, Scheme 2, E = Me), three additional compounds were identified: the rearomatized derivatives **7a** (10%) and **7b** (15%) and the *ortho*-methylated phosphinamide **8** (7%) (Figure 1).[18] The rearomatization observed may

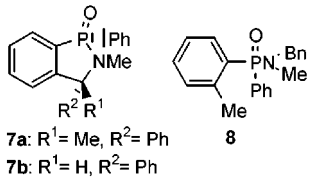
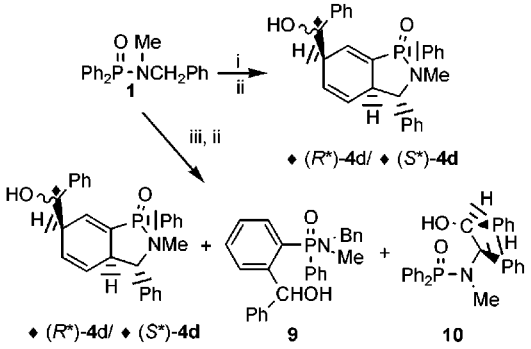


Figure 1.

be a consequence of the workup procedure. However, the reasons for this particular behavior are not clear at present.

The use of benzaldehyde as electrophile is remarkable. With HMPA in the medium, epimers (*S**)-**4d** (δ_P 31.13) and (*R**)-**4d** (δ_P 31.22) were obtained[19] quantitatively in an 80:20 ratio. Interestingly, the use of DMPU as cosolvent afforded similar results (Scheme 3). This implies that when

Scheme 3[a]



[a] i. Bu^{s}Li (1.5 equiv), THF −90 °C, HMPA or DMPU (6 equiv), 30 min; ii. PhCHO, 120 min; iii. Bu^{s}Li (1.5 equiv), THF −90 °C, 30 min.

starting with achiral reagents two new compounds are formed containing five stereogenic centers i.e., only 2 out of 16 possible diastereoisomers! To our delight they could be separated by flash chromatography (ethyl acetate:hexane 2:1).

According to NMR data the two isomers resulted from the nucleophilic attack to the two faces of the carbonyl group, all other stereocenters being the same. The X-ray structure of the mixture (*R**)-**4d**:(*S**)-**4d** confirmed this point and allowed for assignment of the configuration of the hydroxylic carbon of both epimers (Figure 2).[20]

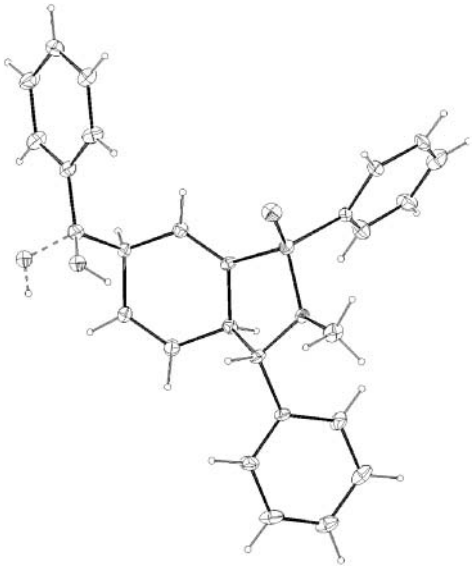


Figure 2. ORTEP type plot of the molecular structure of the mixture of epimers (*R**)-**4d**:(*S**)-**4d**, 38:62. Two alternative positions for the disordered oxygen linked to the benzylic carbon are shown. The dashed C—O bond corresponds to the major isomer (*S**)-**4d**.

In the absence of HMPA, the yield decreased to 72% and small amounts of compounds **9** (mixture of epimers in the COH carbon) and **10** (Scheme 3) were observed. They arise, respectively, from the addition of PhCHO to the *ortho* position of a *P*-phenyl ring and to the benzylic carbon of **1**.[21]

The dearomatized compounds **3**−**4** can be viewed as masked γ-*N*-methylaminophosphinic acids. The solvolysis of the P−N bond is practically instantaneous with aqueous 2 N HCl in acetone and dry 0.6 N HCl in MeOH at room temperature, affording stereospecifically and quantitatively the corresponding γ-(*N*-methylamino)phosphinic acids **11**−**12** and methyl esters **13**−**14**, respectively, with inversion at the phosphorus center (Scheme 4).[22]

(17) The ^{31}P signal of HMPA in $\mathbf{2}_{\mathbf{HMPA}}$ and free HMPA are overlapped.

(18) The compounds were separated by careful flash chromatography using ethyl 2:1 acetate:hexane as eluent. Other byproducts: *cis*-**3a** (1%), **4a** (9%), and $Ph_2P(O)C(Me)_2CH_2CH_3$ (8%) (formed by nucleophilic attack of Bu^{s}Li to **1** followed by metalation and subsequent addition of IMe).

(19) Only the configuration of the stereogenic center labeled in Scheme 3 is given.

(20) (*R**)-**4d**:(*S**)-**4d** crystallized as a mixture with the same ratio (38:62) of isomers found in solution through NMR. The major isomer exhibits an *S* configuration at the starred carbon and is characterized by a δ_P 31.13 ppm and a melting point of 201−202 °C. The corresponding values for (*R**)-**4d** are δ_P 31.22 ppm, mp 189−190 °C.

(21) The formation of compounds **8** and **10** suggests that the anionic cyclization may proceed, at least in part, from an initial *ortho* lithiation of a *P*-phenyl ring which would then intramolecularly deprotonate the benzylic carbon necessary for the cyclodearomatization, as elegantly demonstrated by Clayden et al. for the dearomatization of *N*-benzylnaphthamides. Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103. We are currently studying the mechanism of this reaction.

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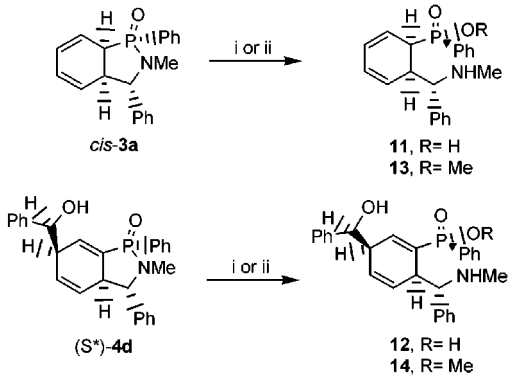
Scheme 4[a]



[a] i. 2 N HCl(H_2O), Me_2CO; ii. 0.6 N HCl(g), MeOH.

γ-Aminophosphinic acids and their derivatives are important target molecules as inhibitors, analogues of 4-aminobutiric acid (GABA) and glutamic acid.[23] The natural tripeptide bialaphos is an antibiotic and commercial herbicide containing the γ-aminophosphinic acid phosphinothricin.[24] However, there are very few syntheses of this type of compounds,[25] and these are generally nonstereoselective.[26]

The new dearomatization reaction reported here is a highly stereoselective and high-yield procedure which allows for the conversion of readily available aromatic compounds to functionalized cyclohexadiene derivatives. Furthermore, it represents an easy entry to the preparation of γ-(*N*-methylamino)phosphinic acids and esters using low cost commercial reagents in a very simple one-pot process. Further applications of the new methodology are in progress.

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Supporting Information Available: Scheme S1, synthetic procedures and characterization of **1** and **3**−**14**, X-ray figure and structural information on (*R**)-**4d**/(*S**)-**4d**, ^{1}H and ^{31}P NMR spectra of **12** and **14**, and ^{31}P NMR spectrum of **2-2**$_{\mathbf{HMPA}}$ measured at −80 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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