Unprecedented asymmetric induction through configurationally stable lithium *N*-(α-methylbenzyl)phosphinamides. A new entry to enantiomerically pure γ-aminophosphinic acids and esters†‡

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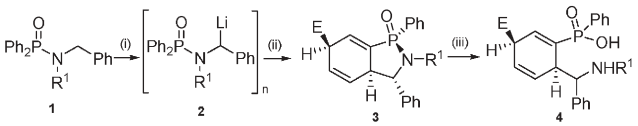
The first examples of configurationally stable *N*-benzyl-*N*-phosphinoyl carbanions are described. Their applications to the synthesis of homochiral γ-aminophosphinic acids and esters *via* highly enantioselective dearomatising reactions are shown.

Chiral, nonracemic, configurationally stable organolithium species are valuable reagents in asymmetric synthesis owing to their ability to form carbon–carbon bonds, often with a high degree of enantioselectivity. Many dipole-stabilised *N*-benzyl and *N*-allyl carbanions showing these characteristics are known.[1] Generally, the stabilisation is provided by a carbonyl group linked to the nitrogen atom.[2] The phosphoramide group is also very efficient in promoting the metalation at a *N*-benzylic position and the synthetic utility of these anions has been extensively studied.[3] However, the applications of chiral anions of *N*-benzylphosphoric triamides have been limited to the alkylation and stannylation of derivatives containing *rac-trans*-1,2-cyclohexanediamine as a chiral auxiliary.[4]

We have previously reported that the lithiation of *N*-benzyl-*N*-methyldiphenylphosphinamide (**1a**, R^1 = Me) in Et_2O solution gives rise to a mixture of monomeric and dimeric benzylic anions **2**.[5] In THF as solvent, these anions evolve through a dearomatising cyclisation reaction[6] leading after electrophilic quench to tetrahydrobenzoazaphospholes **3**.[7] These heterocycles were smoothly transformed into γ-amino phosphinic acids **4** and esters,[8] a class of compounds showing promising antitumor activity and potential scaffolds for the synthesis of γ-phosphapeptides (Scheme 1). Support for the feasibility of asymmetric induction in this process is provided by the work of Clayden and co-workers on the analogous anionic dearomatisation of *N*-(α-methylbenzyl)benzamides.[9]

In this paper we describe the application of the dearomatising anionic cyclisation–alkylation sequence to chiral phosphinamides **5**. The process affords homochiral tetrahydrobenzoazaphospholes in which the P–N linkage could be easily solvolysed to give γ-amino phosphinic acid and ester derivatives. The later being interesting building blocks for γ-peptide chemistry.

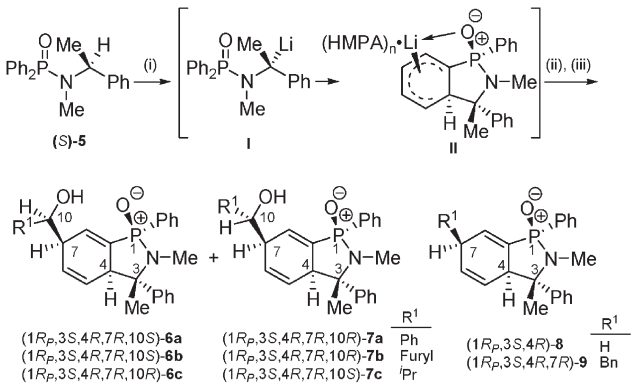


Scheme 1 Dearomatising cyclisation of *N*-benzylphosphinamides **1**. *Reagents:* (i) *t*-BuLi, Et_2O, −90 °C; (ii) THF, DMPU (6 equiv.), −90 °C, then E^+; (iii), H_3O^+.

Racemic-, (*S*)-, and (*R*)-phosphinamides **5** were readily prepared in high yield by reaction of the corresponding α-methylbenzylamine with $Ph_2P(O)Cl$ in toluene in the presence of triethylamine, followed by deprotonation of the resulting phosphinamide with NaH in THF and methylation with MeI.

Under optimised reaction conditions the lithiation of (*S*)-**5** with *t*-BuLi in THF at −90 °C in the presence of 6 equivalents of HMPA and subsequent anionic cyclisation was complete in about 1 min. The instantaneous trapping reaction of the dearomatised species with benzaldehyde furnished a mixture of two azaphospholes **6a** and **7a** (ratio 90:10) epimers in the hydroxylic carbon in a yield of 93% (Scheme 2, see Table S1 in ESI). Increasing the quenching time to 1 min produced the almost quantitative conversion of (*S*)-**5** with a slight decrease in the diastereomeric ratio (Table 1, entry 7).

The reactions with furfural and isobutyraldehyde as electrophiles proceed in the same manner, although with slightly lower yields and diastereoselectivities (Table 1, entries 8, 9). In the



Scheme 2 Dearomatising cyclisation of (*S*)-**5**. *Reagents:* (i) *t*-BuLi, THF, HMPA (6 equiv.), −90 °C, 1 min; (ii) $E^+ = R^1CHO$ (R^1 = Ph, Furyl, ^{i}Pr), 2,6-di-*tert*-butyl-4-methylphenol, BnBr, 1 min; (iii) MeOH–H_2O.

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† Dedicated to Professor Joaquín Plumet on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: optimisation study of the dearomatising cyclisation reaction, synthetic procedures, and NMR characterisation of **6a–c**, **10**, **11**, and **12**. HPLC chromatograms of *rac*-**6b**, **8**, **9**, and **6b**, **8**, **9**. 2D gNOESY spectra and selected rows of **10**, **11**. ^1H, $^1H\{^{31}P\}$ NMR spectra of **12** and **13**. See DOI: 10.1039/b510685k

Table 1 Distribution of products in the dearomatising anionic cyclisation–alkylation of chiral *N*-α-methylbenzylphosphinamides[a]

Entry	Reagent	E^+	Product	Yield (%)[b]	**6** : **7**[c]	ee (%)[d]
1	*rac*-**5**	PhCHO	*rac*-**6a/7a**	98	88 : 12	
2	*rac*-**5**	PhCHO	*rac*-**6a/7a**	6[e]		
3	*rac*-**5**	C_4H_3OCHO	*rac*-**6b/7b**	91	81 : 19	
4	*rac*-**5**	$(CH_3)_2CHCHO$	*rac*-**6c/7c**	78	69 : 31	
5	*Rac*-**5**	ArOH	*rac*-**8**	77		
6	*rac*-**5**	$BrCH_2Ph$	*rac*-**9**	84[e,f]		
7	(*S*)-**5**	PhCHO	**6a/7a**	98	88 : 12	>99
8	(*S*)-**5**	C_4H_3OCHO	**6b/7b**	91	81 : 19	>99
9	(*S*)-**5**	$(CH_3)_2CHCHO$	**6c/7c**	78	68 : 32	95
10	(*R*)-**5**	PhCHO	*ent*-**6a/7a**	97	89 : 11	>99
11	(*S*)-**5**	ArOH	**8**	74		>99
12	(*R*)-**5**	ArOH	*ent*-**8**	73		>99
13	(*S*)-**5**	$BrCH_2Ph$	**9**	84[e,f]		>99
14	(*R*)-**5**	$BrCH_2Ph$	*ent*-**9**	80[e,f]		>99

[a] All reactions were carried on a 20 mM scale using 1 min. of lithiation and 1 min. with E^+. [b] Crude yield. [c] Ratio of (*S*) : (*R*) epimers in the exocyclic methine. Separated by column chromatography except **6b**, which precipitated from ether. [d] Ee determined by chiral HPLC. For further details see ESI. [e] DMPU was used as cosolvent. [f] 12 h of lithiation and 30 min reacting with the E^+. A minor diastereoisomer (<8%) epimer in the phosphorus atom was also isolated.

reaction with isobutyraldehyde small amounts (<4%) of a compound epimer of **6c** in the phosphorus atom were also formed. As expected, the analogous reactions of phosphinamides (*R*)-**5** and *rac*-**5** provided *ent*-**6–7** and racemic **6–7**, respectively (Table 1). Surprisingly, the reaction practically failed when DMPU was used as cosolvent under otherwise the same reaction conditions (Table 1, entry 2).

All the tetrahydrobenzoazaphospholes **6–7** were conveniently isolated by column chromatography except **6b**, which precipitated from Et_2O. The enantiomer ratios of **6–7** were determined using chiral HPLC. In all cases very high enantiomeric excesses were found (Table 1).

All new compounds were fully characterised based on their 1D and 2D NMR data. Attack of the electrophile at the γ position to the phosphorus is evidenced by the large deshielding and couplings to the phosphorus observed for the CH=CP(O)N moiety in the ^1H and ^{13}C NMR spectra ($\delta_H \sim 6.6$ ppm, $^3J_{PH} \sim 17$ Hz, $\delta_C \sim 133$ ppm, $^1J_{PC} \sim 120$ Hz).§ Additionally, the magnitude of the ^{31}P chemical shifts of heterocycles **6–7** about 30 ppm is typical of γ-alkylated tetrahydrobenzoazaphospholes.[8] The absolute configuration was deduced by the analysis of the 2D NOESY spectra of the esters **10** and **11** derived from the reaction of **6b** and *ent*-**6b** with the (*R*)-Mosher reagent, respectively (Fig. 1). The NOEs observed indicate that the lithiation–cyclisation sequence went with complete retention of the configuration of the original chiral center. It implies that the open chain benzylic carbanion is configurationally stable on the timescale of the cyclisation and very efficiently transmits the chiral information to four new stereogenic centers, two of them notably apart from the origin of chirality. It is also remarkable the fact that the asymmetric induction process involves the exclusive attack to one of the two diastereotopic *P*-phenyl rings.

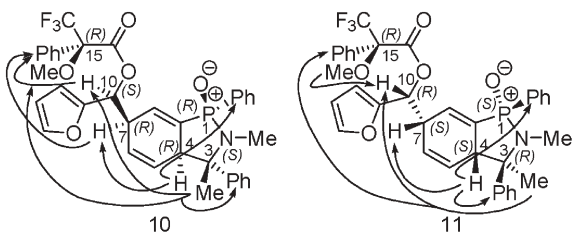


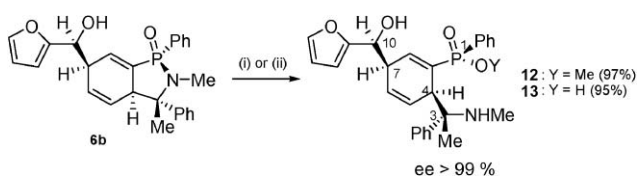
Fig. 1 Selected NOEs observed for (1R_P,3*S*,4*R*,7*R*,10*S*,15*R*)-**10** and (1S_P,3*R*,4*S*,7*S*,10*R*,15*R*)-**11**.

The dearomatisation–alkylation sequence of phosphinamides **5** was extended to include 2,6-di-*tert*-butyl-4-methylphenol and benzylbromide as electrophiles. The protonation with the hindered phenol proceeded in good yield to give azaphospholes **8** (Table 1, entries 5, 11, 12). The alkylation with BnBr required some optimisation. High yields of *rac*-**9** and enantiopure compounds **9** and *ent*-**9** were obtained when DMPU was used as cosolvent and the times for metalation and quenching were increased to 12 h and 30 min, respectively (Table 1, entries 6, 13, 14). In both cases a minor diastereoisomeric (<8%) epimer in the phosphorus atom was also formed. Column chromatography allowed the isolation of the major pure compounds. NOE measurements of the new products showed that the stereochemical course of the process was the same observed for azaphospholes **6**.

We have previously shown that tetrahydrobenzoazaphospholes can be converted quantitatively into γ-aminophosphinic acids and esters by solvolysis of the P–N bond.[8] Such compounds and their derivatives are important bioactive targets as inhibitors analogues of 4-aminobutyric acid (GABA) and glutamic acid.[10] However, only few syntheses, and generally non stereoselective, of this type of compounds have been described.[11]

Treating **6b** with HCl in dry methanol produced the stereospecific formation of the aminophosphinic ester **12** in almost quantitative yield. Attack of methanol to the phosphorus center of the phosphinamide linkage is assumed to proceed with inversion of the configuration as described in the literature (Scheme 3).[8a,12] The corresponding acid **13** was obtained by performing the hydrolysis of **6b** with diluted hydrochloric acid in acetone.

In summary, the sequential dearomatisation–alkylation reported here is a highly diastereo- and enantioselective and high yield procedure, which allows the synthesis of enantiomerically pure functionalized [1,4]-cyclohexadiene derivatives, and constitutes the first example of a configurationally stable tertiary lithiated benzylic carbanion dipolarly stabilised by a phophinamide group. This carbanion undergoes cascade reactions which proceed with a large degree of both retention and transmission of the chiral information, even to remote centers of the system. Furthermore, simply solvolysis of the dearomatised products gives access to the preparation of enantiomerically pure γ-*N*-methylamino phosphinic acids and esters in high yields, which represents an easy entry to phosphorus-containing γ-peptide mimetics. This chemistry and their applications as antitumour agents is under exploration.



Scheme 3 Stereospecific synthesis of an enantiomerically pure γ aminophosphinic acid and ester. *Reagents:* for (1R_P,3*S*,4*R*,7*R*,10*S*)-**12** (i) 2N HCl, acetone; for (3*S*,4*R*,7*R*,10*S*)-**13** (ii) 0.6 N HCl, dry methanol.

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Notes and references

§ NMR data of **6a** (25 °C, $CDCl_3$): ^1H NMR (300.13 MHz): δ 1.41 (s, H-11), 2.27 (d, 3H, $^3J_{PH}$ 9.2 Hz, H-12), 2.98 (ddddd, 1H, $^3J_{PH}$ 2.2, $^5J_{HH}$ 11.4 $^3J_{HH}$ 4.0, $^3J_{HH}$ 3.9, $^4J_{HH}$ 1.8 Hz, H-7), 3.40 (ddd, 1H, $^5J_{HH}$ 11.4, $^4J_{HH}$ 4.4, $^3J_{HH}$ 2.2 Hz, H-4), 3.84 (bs, OH, H-13), 4.98 (d, 1H, $^3J_{HH}$ 3.9 Hz, H-10), 5.49 (ddt, 1H, $^4J_{PH}$ 4.4, $^3J_{HH}$ 10.4, $^3J_{HH}$ 2.2 Hz, H-5), 5.75 (m, 1H, $^3J_{HH}$ 10.4, $^4J_{HH}$ 4.0, $^3J_{HH}$ 2.2 Hz, H-6), 6.79 (ddd, 1H, $^3J_{PH}$ 17.2, $^3J_{HH}$ 4.0, $^4J_{HH}$ 1.8 Hz, H-8), 7.63-7.22 (m, 8H, ArH), 7.92 (m, 2H, H-15). ^{13}C NMR (75.47 MHz): δ 18.35 (C-11), 25.26 (d, $^2J_{PC}$ 3.0 Hz, C-12), 44.75 (d, $^3J_{PC}$ 12.0 Hz, C-7), 52.46 (d, $^2J_{PC}$ 13.8 Hz, C-4), 66.84 (d, $^2J_{PC}$ 10.2 Hz, C-3), 75.70 (C-10), 123.41 (d, $^3J_{PC}$ 6.6 Hz, C-5), 126.51 (d, $^4J_{PC}$ 1.8 Hz, C-6), 128.61–126.48 (12CAr), 131.71 (d, $^4J_{PC}$ 3.0 Hz, C-17), 131.83 (d, $^2J_{PC}$ 10.2 Hz, C-15), 132.88 (d, $^1J_{PC}$ 134.6 Hz, C-14), 134.49 (d, $^1J_{PC}$ 120.1 Hz, C-9), 137.53 (d, $^2J_{PC}$ 9.6 Hz, C-8), 141.65 (C-18), 142.83 (d, $^3J_{PC}$ 8.4 Hz, C-22). ^{31}P NMR (121.50 MHz): δ 29.12. MS (APCI): *m/z* 442 (M + 1, 100%).

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